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Questions General Medical Council General Medical Council Lab Values, Normal Adult:...

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Incidence and prevalence

These two terms are used to describe the frequency of a condition in a population.

The **incidence** is the number of new cases per population in a given time period.

For example, if condition X has caused 40 new cases over the past 12 months per 1,000 of the population the annual incidence is 0.04 or 4%.

The **prevalence** is the total number of cases per population at a particular point in time.

For example, imagine a questionnaire is sent to 2,500 adults asking them how much they weigh. If from this sample population of 500 of the adults were obese then the prevalence of obesity would be 0.2 or 20%.

Relationship

- prevalence = incidence * duration of condition
- in chronic diseases the prevalence is much greater than the incidence
- in acute diseases the prevalence and incidence are similar. For conditions such as the common cold the incidence may be greater than the prevalence

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Questions

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Provide a graphical representation of the relative risk results in a cohort study 15%

Provide a graphical representation of the probability of a patient experiencing a particular adverse effect 12%

Funnel plots - show publication bias in meta-analyses



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Funnel plot

A funnel plot is primarily used to demonstrate the existence of publication bias in meta-analyses. Funnel plots are usually drawn with treatment effects on the horizontal axis and study size on the vertical axis.

Interpretation

- a symmetrical, inverted funnel shape indicates that publication bias is unlikely
- conversely, an asymmetrical funnel indicates a relationship between treatment effect and study size. This indicates either publication bias or a systematic difference between smaller and larger studies ('small study effects')

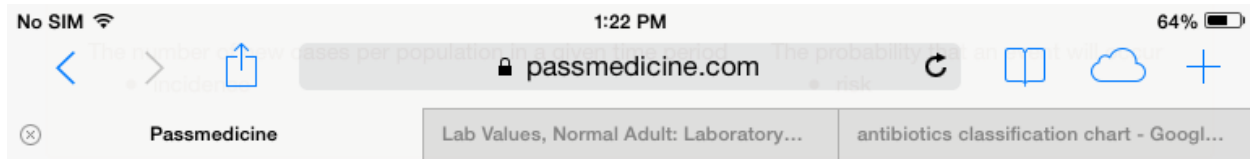
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Statistical terms: descriptive statistics

The table below gives a brief definition of commonly encountered terms:

Term	Description
Mean	The average of a series of observed values
Median	The middle value if series of observed values are placed in order
Mode	The value that occurs most frequently within a dataset
Range	The difference between the largest and smallest observed value

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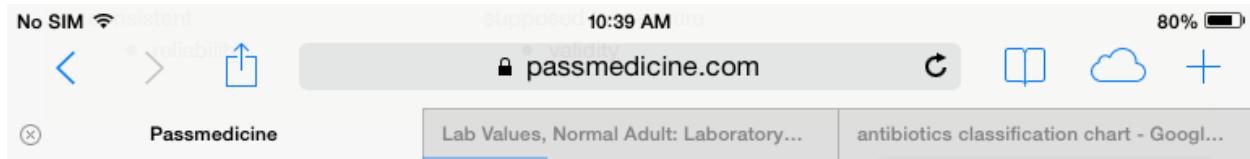
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Mean - the average of a series of observed values

Notes (1/1)

Cushing's syndrome causes hypokalaemia

Notes (0/1)



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Reliability and validity

Reliability is used in statistics to imply consistency.

Validity is determined by whether a test accurately measures what it is supposed to measure.

Reliability and validity are independent of each other. A measurement can be valid but not reliable, or reliable but not valid. For example, if a pulse oximeter records the oxygen saturations 5% below the true value every time it is used then from a statistical point of view it is 'reliable' (the value is consistently 5% below the true value) but not 'valid' (as the reported saturations are not an accurate reflection of the true values).

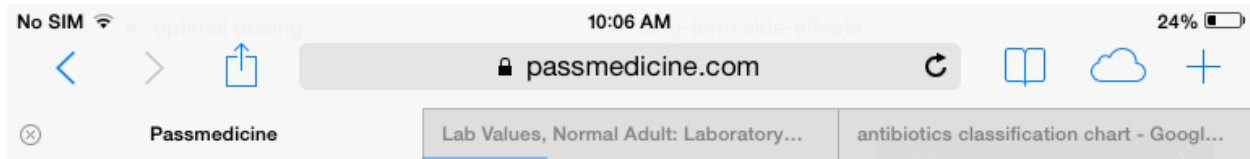
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Clinical trial: phases

Clinical trials are commonly classified into 4 phases;

Phase	Goal	Notes
I	Determines pharmacokinetics and pharmacodynamics and side-effects prior to larger studies	Conducted on healthy volunteers
II	Assess efficacy + dosage	Involves small number of patients affected by particular disease May be subdivided into - IIa - assesses optimal dosing - IIb - assesses efficacy
III	Assess effectiveness	Typically involves 100-1000's of people, often as part of a randomised controlled trial, comparing new treatment with established treatments
IV	Postmarketing surveillance	Monitors for long-term effectiveness and side-effects

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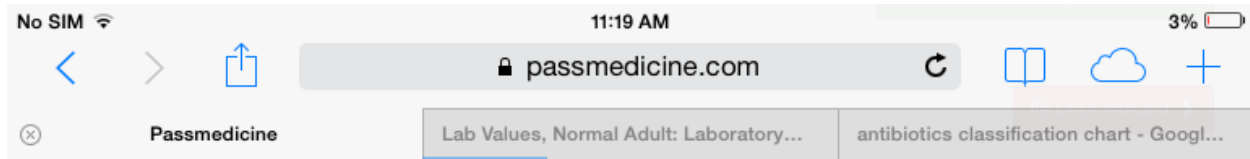









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Odds and odds ratio

Odds are a ratio of the number of people who incur a particular outcome to the number of people who do not incur the outcome. The odds ratio may be defined as the ratio of the odds of a particular outcome with experimental treatment and that of control.

Odds vs. probability

In contrast, probability is the fraction of times you'd expect to see an event in many trials. When expressed as a single number probability is always between 0 and 1. So, if we take the example of rolling a dice:

- the probability of rolling a six is $1/6$ or 0.166666
- the odds of rolling a six is $1/5$ or 0.2

Odds ratios are the usual reported measure in case-control studies. It approximates to relative risk if the outcome of interest is rare.

For example, if we look at a trial comparing the use of paracetamol for dysmenorrhoea compared to placebo we may get the following results

	Total number of patients	Achieved = 50% pain relief
Paracetamol	60	40
Placebo	90	30

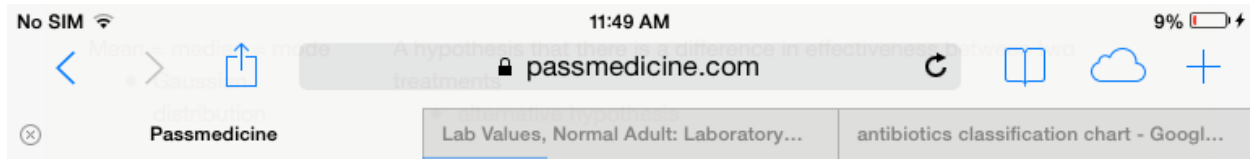
The odds of achieving significant pain relief with paracetamol = $40 / 20 = 2$

The odds of achieving significant pain relief with placebo = $30 / 60 = 0.5$

Therefore the odds ratio = $2 / 0.5 = 4$

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Skewed distributions

Normal (Gaussian) distributions: mean = median = mode

Positively skewed distribution: mean > median > mode

Negatively skewed distribution mean < median < mode

To remember the above note how they are in alphabetical order, think positive going forward with '>', whilst negative going backwards '<'

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Bias

Bias describes the situation in a trial where one outcome is systematically favoured. It should be noted that there is considerable variation in the definitions and classification of bias. The table below lists some of the more common types of bias.

Type	Description
Selection bias	Error in assigning individuals to groups leading to differences which may influence outcome. Subtypes include sampling bias where the subjects are not representative of the population. This may be due to volunteer bias. An example of volunteer bias would be a study looking at the prevalence of <i>Chlamydia</i> in the student population. Students who are at risk of <i>Chlamydia</i> may be more, or less, likely to participate in the study. A similar concept is non-responder bias. If a survey on dietary habits was sent out in the post to random households it is likely that the people who didn't respond would have poorer diets than those who did. Other examples include • loss to follow up bias • prevalence/incidence bias (Neyman bias): when a study is investigating a condition that is characterised by early fatalities or silent cases. It results from missed cases being omitted from calculations • admission bias (Berkson's bias): cases and controls in a hospital case control study are systematically different from one another because the combination of exposure to risk and occurrence of disease increases the likelihood of being admitted to the hospital • healthy worker effect
Recall bias	Difference in the accuracy of the recollections retrieved by study participants, possibly due to whether they have disorder or not. E.g. a patient with lung cancer may search their memories more thoroughly for a history of asbestos exposure than someone in the control group. A particular problem in case-control studies.
Publication bias	Failure to publish results from valid studies, often as they showed a negative or uninteresting result. Important in meta-analyses where studies showing negative results may be excluded.
Work-up bias (verification bias)	In studies which compare new diagnostic tests with gold standard tests, work-up bias can be an issue. Sometimes clinicians may be reluctant to order the gold standard test unless the new test is positive, as the gold standard test may be invasive (e.g. tissue biopsy). This approach can seriously distort the results of a study, and alter values such as specificity and sensitivity. Sometimes work-up bias cannot be avoided, in these cases it must be adjusted for by the researchers.
Expectation bias (Pygmalion effect)	Only a problem in non-blinded trials. Observers may subconsciously measure or report data in a way that favours the expected study outcome.

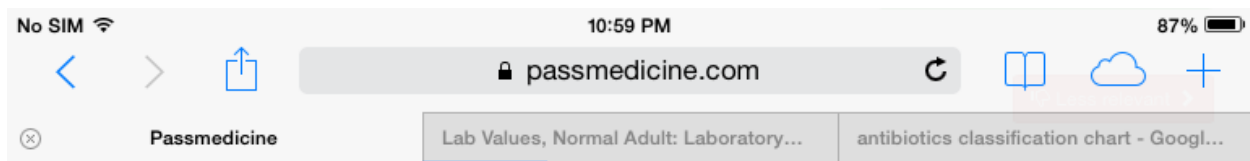
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bias)	seriously distort the results of a study, and alter values such as specificity and sensitivity. Sometimes work-up bias cannot be avoided, in these cases it must be adjusted for by the researchers.
Expectation bias (Pygmalion effect)	Only a problem in non-blinded trials. Observers may subconsciously measure or report data in a way that favours the expected study outcome.
Hawthorne effect	Describes a group changing it's behaviour due to the knowledge that it is being studied
Late-look bias	Gathering information at an inappropriate time e.g. studying a fatal disease many years later when some of the patients may have died already
Procedure bias	Occurs when subjects in different groups receive different treatment
Lead-time bias	Occurs when two tests for a disease are compared, the new test diagnoses the disease earlier, but there is no effect on the outcome of the disease

Selection bias	Error in assigning individuals to groups leading to differences which may influence outcome. Subtypes include sampling bias where the subjects are not representative of the population. This may be due to volunteer bias. An example of volunteer bias would be a study looking at the prevalence of Chlamydia in the student population. Students who are at risk of Chlamydia may be more, or less, likely to participate in the study. A similar concept is non-responder bias. If a survey on dietary habits was sent out in the post to random households it is likely that the people who didn't respond would have poorer diets than those who did. Other examples include loss to follow up bias, prevalence/incidence bias aka Neyman bias, admission bias aka Berkson's bias, healthy worker effect)
Information bias	A form of bias that occurs when measurement of information differs among study groups examples include recall bias, reporting bias, diagnostic bias, and Hawthorne effect, errors in measurement
Publication bias	Failure to publish results from valid studies, often as they showed a negative or uninteresting result. Important in meta-analyses where studies showing negative results may be excluded
Confounding bias	Distortion of exposure, disease relation by some other factor



Study design

The following table highlights the main features of the main types of study:

Study type	Key features
Randomised controlled trial	Participants randomly allocated to intervention or control group (e.g. standard treatment or placebo) Practical or ethical problems may limit use
Cohort study	Observational and prospective. Two (or more) are selected according to their exposure to a particular agent (e.g. medicine, toxin) and followed up to see how many develop a disease or other outcome. The usual outcome measure is the relative risk. Examples include Framingham Heart Study
Case-control study	Observational and retrospective. Patients with a particular condition (cases) are identified and matched with controls. Data is then collected on past exposure to a possible causal agent for the condition. The usual outcome measure is the odds ratio. Inexpensive, produce quick results Useful for studying rare conditions Prone to confounding
Cross-sectional survey	Provide a 'snapshot', sometimes called prevalence studies Provide weak evidence of cause and effect

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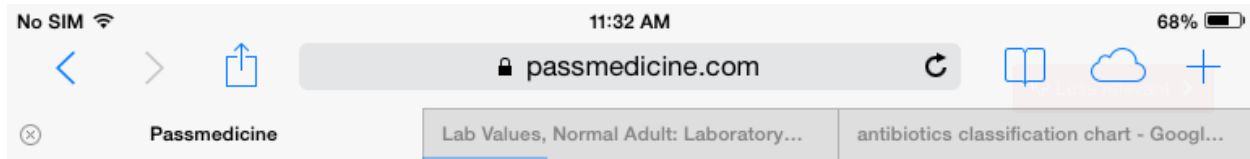
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Significance tests

A null hypothesis (H_0) states that two treatments are equally effective (and is hence negatively phrased). A significance test uses the sample data to assess how likely the null hypothesis is to be correct.

For example:

- 'there is no difference in the prevalence of colorectal cancer in patients taking low-dose aspirin compared to those who are not'

The alternative hypothesis (H_1) is the opposite of the null hypothesis, i.e. There is a difference between the two treatments

The **p value** is the probability of obtaining a result by chance at least as extreme as the one that was actually observed, assuming that the null hypothesis is true. It is therefore equal to the chance of making a type I error (see below).

Two types of errors may occur when testing the null hypothesis

- type I: the null hypothesis is rejected when it is true - i.e. Showing a difference between two groups when it doesn't exist, a false positive. This is determined against a preset significance level (termed alpha). As the significance level is determined in advance the chance of making a type I error is not affected by sample size. It is however increased if the number of end-points are increased. For example if a study has 20 end-points it is likely one of these will be reached, just by chance.
- type II: the null hypothesis is accepted when it is false - i.e. Failing to spot a difference when one really exists, a false negative. The probability of making a type II error is termed beta. It is determined by both sample size and alpha

	Study accepts H_0	Study rejects H_0
Reality H_0		Type 1 error (alpha)
Reality H_1	Type 2 error (beta)	Power (1 - beta)

The power of a study is the probability of (correctly) rejecting the null hypothesis when it is false, i.e. the probability of detecting a statistically significant difference

- power = 1 - the probability of a type II error
- power can be increased by increasing the sample size



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Significance tests: types

The type of significance test used depends on whether the data is parametric (something which can be measured, usually normally distributed) or non-parametric

Parametric tests

- Student's t-test - paired or unpaired*
- Pearson's product-moment coefficient - correlation

Non-parametric tests

- Mann-Whitney U test - unpaired data
- Wilcoxon signed-rank test - compares two sets of observations on a single sample
- chi-squared test - used to compare proportions or percentages
- Spearman, Kendall rank - correlation

*paired data refers to data obtained from a single group of patients, e.g. Measurement before and after an intervention. Unpaired data comes from two different groups of patients, e.g. Comparing response to different interventions in two groups

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Screening test statistics

Patients and doctors need to know if a disease or condition is present or absent. Tests can be used to help us decide. Tests generally guide us by indicating how likely it is that the patient has the condition.

In order to interpret test results we need to have a working knowledge of the statistics used to describe them.

Contingency tables (also known as 2 * 2 tables, see below) are used to illustrate and calculate test statistics such as sensitivity. It would be unusual for a medical exam not to feature a question based around screening test statistics. Commit the following table to memory and spend time practicing using it as you will be expected to make calculations using it in your exam.

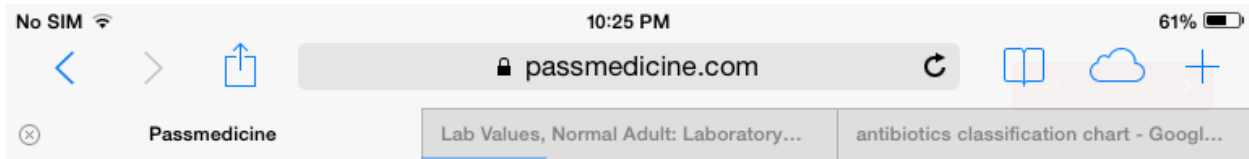
TP = true positive; FP = false positive; TN = true negative; FN = false negative

	Disease present	Disease absent
Test positive	TP	FP
Test negative	FN	TN

The table below lists the main statistical terms used in relation to screening tests:

Measure	Formula	Plain english
Sensitivity	$TP / (TP + FN)$	Proportion of patients with the condition who have a positive test result
Specificity	$TN / (TN + FP)$	Proportion of patients without the condition who have a negative test result
Positive predictive value	$TP / (TP + FP)$	The chance that the patient has the condition if the diagnostic test is positive
Negative predictive value	$TN / (TN + FN)$	The chance that the patient does not have the condition if the diagnostic test is negative
Likelihood ratio for a positive test result	$sensitivity / (1 - specificity)$	How much the odds of the disease increase when a test is positive
Likelihood ratio for a negative test result	$(1 - sensitivity) / specificity$	How much the odds of the disease decrease when a test is negative

Positive and negative predictive values are prevalence dependent. Likelihood ratios are not prevalence dependent.



Correlation and linear regression

The terms correlation and regression are related but are not synonymous. Correlation is used to test for association between variables (e.g. whether salary and IQ are related). Once correlation between two variables has been shown regression can be used to predict values of other dependent variables from independent variables. Regression is not used unless two variables have firstly been shown to correlate.

Correlation

The degree of correlation is summarised by the correlation coefficient (r). This indicates how closely the points lie to a line drawn through the plotted data. In parametric data this is called Pearson's correlation coefficient and can take any value between -1 to $+1$.

For example

- $r = 1$ - strong positive correlation (e.g. systolic blood pressure always increases with age)
- $r = 0$ - no correlation (e.g. there is no correlation between systolic blood pressure and age)
- $r = -1$ - strong negative correlation (e.g. systolic blood pressure always decreases with age)

Whilst correlation coefficients give information about how one variable may increase or decrease as another variable increases they do not give information about how much the variable will change. They also do not provide information on cause and effect.

Correlation is summarised when using parametric variables by Pearson's correlation coefficient (represented by a small r). In the situation of non parametric variables, Spearman's correlation coefficient is used. Spearman's correlation coefficient is usually represented by the Greek letter ρ (rho), or by r_s .

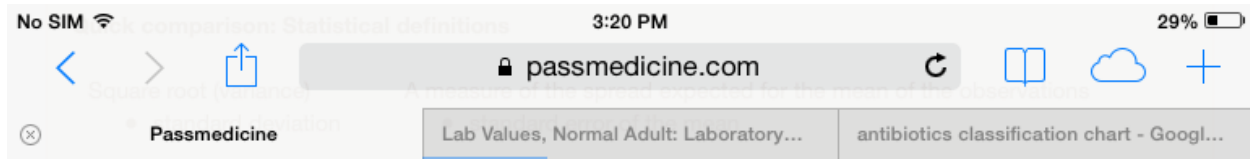
In the case of dichotomous variables logistic regression is used. Linear (or simple linear) regression is used when looking for association between two continuous variables, and multiple regression is used when looking for association between more than two continuous variables.

Linear regression

In contrast to the correlation coefficient, linear regression may be used to predict how much one variable changes when a second variable is changed. A regression equation may be formed, $y = a + bx$, where

- y = the variable being calculated
- a = the intercept value, when $x = 0$
- b = the slope of the line or regression coefficient. Simply put, how much y changes for a given change in x
- x = the second variable





Normal distribution

The normal distribution is also known as the Gaussian distribution or 'bell-shaped' distribution. It describes the spread of many biological and clinical measurements

Properties of the Normal distribution

- symmetrical i.e. Mean = mode = median
- 68.3% of values lie within 1 SD of the mean
- 95.4% of values lie within 2 SD of the mean
- 99.7% of values lie within 3 SD of the mean
- this is often reversed, so that within 1.96 SD of the mean lie 95% of the sample values
- the range of the mean - (1.96 * SD) to the mean + (1.96 * SD) is called the 95% confidence interval, i.e. If a repeat sample of 100 observations are taken from the same group 95 of them would be expected to lie in that range

Standard deviation

- the standard deviation (SD) is a measure of how much dispersion exists from the mean
- SD = square root (variance)

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The confidence interval is a common and sometimes misunderstood principle in medical statistics.

- a formal definition may be: *a range of values for a variable of interest constructed so that this range has a specified probability of including the true value of the variable. The specified probability is called the confidence level, and the end points of the confidence interval are called the confidence limits**
- in simpler terms: a range of values within which the true effect of intervention is likely to lie

The likelihood of the true effect lying within the confidence interval is determined by the confidence level. For example a confidence interval at the 95% confidence level means that the confidence interval should contain the true effect of intervention 95% of the time.

How is the confidence interval calculated?

The standard error of the mean (SEM) is a measure of the spread expected for the mean of the observations - i.e. how 'accurate' the calculated sample mean is from the true population mean

Key point

- $SEM = SD / \text{square root } (n)$
- where SD = standard deviation and n = sample size
- therefore the SEM gets smaller as the sample size (n) increases

A 95% confidence interval:

- lower limit = $\text{mean} - (1.96 * SEM)$
- upper limit = $\text{mean} + (1.96 * SEM)$

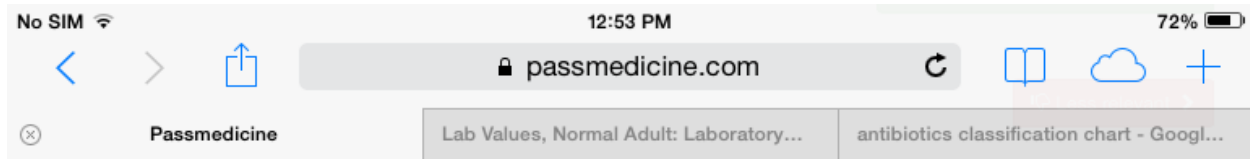
The above formula is a slight simplification:

- if a small sample size is used (e.g. $n < 100$) then it is important to use a 'Student's T critical value' look-up table to replace 1.96 with a different value
- if a different confidence level is required, e.g. 90% then 1.96 is replaced by a different value. For 90% this would be 1.645

Results such as mean value are often presented along with a confidence interval. For example, in a study the mean height in a sample taken from a population is 183cm. You know that the standard error (SE) (the standard deviation of the mean) is 2cm. This gives a 95% confidence interval of 179-187cm (± 2 SE).

*Last JM. A dictionary of epidemiology. Oxford: International Journal of Epidemiology, 1988

Croup guidelines



Confidence interval and standard error of the mean

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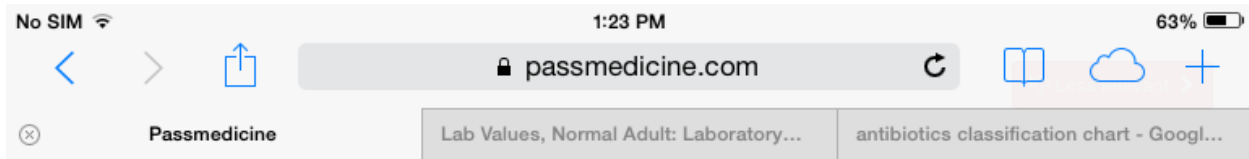
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Questions Lab Values, Normal Adult: Laboratory... antibiotics classification chart - Googl...

IIb 13%

IV 17%

Discuss Improve

Next question >

Study design: evidence and recommendations

Levels of evidence

- Ia - evidence from meta-analysis of randomised controlled trials
- Ib - evidence from at least one randomised controlled trial
- IIa - evidence from at least one well designed controlled trial which is not randomised
- IIb - evidence from at least one well designed experimental trial
- III - evidence from case, correlation and comparative studies
- IV - evidence from a panel of experts

Grading of recommendation

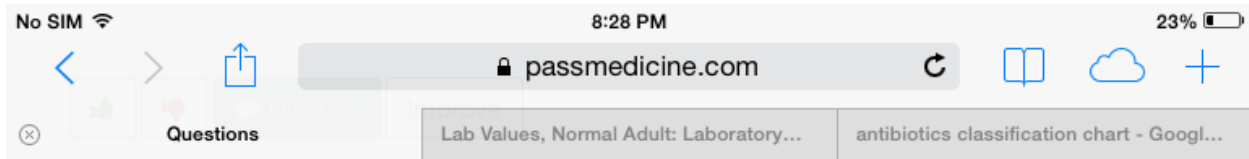
- Grade A - based on evidence from at least one randomised controlled trial (i.e. Ia or Ib)
- Grade B - based on evidence from non-randomised controlled trials (i.e. IIa, IIb or III)
- Grade C - based on evidence from a panel of experts (i.e. IV)

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Study design: new drugs

When a new drug is launched there are a number of options available in terms of study design. One option is a placebo controlled trial. Whilst this may provide robust evidence it may be considered unethical if established treatments are available and it also does not provide a comparison with standard treatments.

If a drug is therefore to be compared to an existing treatment a statistician will need to decide whether the trial is intended to show superiority, equivalence or non-inferiority:

- superiority: whilst this may seem the natural aim of a trial one problem is the large sample size needed to show a significant benefit over an existing treatment
- equivalence: an equivalence margin is defined ($-\delta$ to $+\delta$) on a specified outcome. If the confidence interval of the difference between the two drugs lies within the equivalence margin then the drugs may be assumed to have a similar effect
- non-inferiority: similar to equivalence trials, but only the lower confidence interval needs to lie within the equivalence margin (i.e. $-\delta$). Small sample sizes are needed for these trials. Once a drug has been shown to be non-inferior large studies may be performed to show superiority

It should be remembered that drug companies may not necessarily want to show superiority over an existing product. If it can be demonstrated that their product is equivalent or even non-inferior then they may compete on price or convenience.

Next question >

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Next question >

Pre- and post- test odds and probability

Pre-test probability

The proportion of people with the target disorder in the population at risk at a specific time (point prevalence) or time interval (period prevalence)

For example, the prevalence of rheumatoid arthritis in the UK is 1%

Post-test probability

The proportion of patients with that particular test result who have the target disorder

Post-test probability = post test odds / (1 + post-test odds)

Pre-test odds

The odds that the patient has the target disorder before the test is carried out

Pre-test odds = pre-test probability / (1 - pre-test probability)

Post-test odds

The odds that the patient has the target disorder after the test is carried out

Post-test odds = pre-test odds x likelihood ratio

where the likelihood ratio for a positive test result = sensitivity / (1 - specificity)

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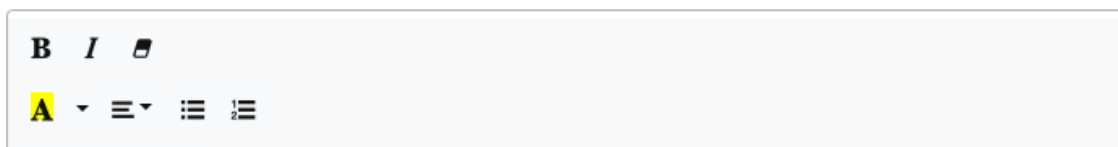


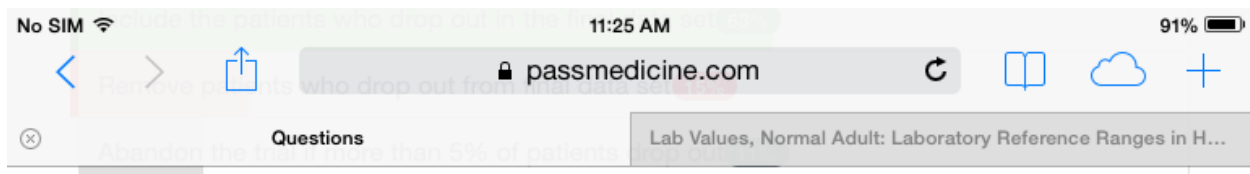
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Screening: Wilson and Junger criteria

1. The condition should be an important public health problem
2. There should be an acceptable treatment for patients with recognised disease
3. Facilities for diagnosis and treatment should be available
4. There should be a recognised latent or early symptomatic stage
5. The natural history of the condition, including its development from latent to declared disease should be adequately understood
6. There should be a suitable test or examination
7. The test or examination should be acceptable to the population
8. There should be agreed policy on whom to treat
9. The cost of case-finding (including diagnosis and subsequent treatment of patients) should be economically balanced in relation to the possible expenditure as a whole
10. Case-finding should be a continuous process and not a 'once and for all' project

Next question >





Next question >

Intention to treat analysis

Intention to treat analysis is a method of analysis for randomized controlled trials in which all patients randomly assigned to one of the treatments are analysed together, regardless of whether or not they completed or received that treatment

Intention to treat analysis is done to avoid the effects of crossover and drop-out, which may affect the randomization to the treatment groups

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Renal tubular acidosis

All three types of renal tubular acidosis (RTA) are associated with hyperchloraemic metabolic acidosis (normal anion gap)

Type 1 RTA (distal)

- inability to generate acid urine (secrete H^+) in distal tubule
- causes hypokalaemia
- complications include nephrocalcinosis and renal stones
- causes include idiopathic, RA, SLE, Sjogren's, amphotericin B toxicity, analgesic nephropathy



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Abdominal x-ray showing nephrocalcinosis - a classical finding in type 1 RTA

Hypernatraemia

Causes of hypernatraemia

- dehydration
- osmotic diuresis e.g. hyperosmolar non-ketotic diabetic coma
- diabetes insipidus
- excess IV saline

Hypernatraemia should be corrected with great caution. Although brain tissue can lose sodium and potassium rapidly, lowering of other osmolytes (and importantly water) occurs at a slower rate, predisposing to cerebral oedema, resulting in seizures, coma and death¹. Although there are no clinical guidelines by NICE or Royal College of Physicians at present, it is generally accepted that a rate of no greater than 0.5 mmol/hour correction is appropriate¹.

1. Reynolds RM, Padfield PL, Seckl JR; Disorders of sodium balance. BMJ. 2006 Mar 25;332(7543):702-5.

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Close

Hyperosmolar non-ketotic diabetic coma causes hypernatraemia

Notes (1/1)

Warfarin in breastfeeding is considered safe to use

Notes (1/1)

Acute intermittent porphyria is autosomal dominant

Notes (0/1)

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Questions General Medical Council General Medical Council Lab Values, Normal Adult:...

Central pontine myelinolysis can occur if hyponatraemia is corrected too rapidly. The other mechanisms are not classically involved in hyponatraemia.

Effects of hyponatraemia on the brain

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4470176/>

👍 👎 Discuss Improve

Next question >

Hyponatraemia: correction

Central pontine myelinolysis

- demyelination syndrome caused by rapid correction of chronic hyponatraemia
- may lead to quadriparesis and bulbar palsy
- diagnosis: MRI brain

Next question >

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Next question >

Hypokalaemia

Potassium and hydrogen can be thought of as competitors. Hyperkalaemia tends to be associated with acidosis because as potassium levels rise fewer hydrogen ions can enter the cells

Hypokalaemia with alkalosis

- vomiting
- diuretics
- Cushing's syndrome
- Conn's syndrome (primary hyperaldosteronism)

Hypokalaemia with acidosis

- diarrhoea
- renal tubular acidosis
- acetazolamide
- partially treated diabetic ketoacidosis

Magnesium deficiency may also cause hypokalaemia. In such cases, normalizing the potassium level may be difficult until the magnesium deficiency has been corrected

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Next question >

Pseudohyperkalaemia

Pseudohyperkalaemia is a rise in serum potassium that occurs due to excessive leakage of potassium from cells, during or after blood is taken. It is a laboratory artefact and does not represent the true serum potassium concentration. The majority of potassium is intracellular and thus leakage from cells can significantly impact serum levels. In this case the potassium is released as the large numbers of platelets aggregate and degranulate.

Causes include:

- haemolysis during venepuncture (excessive vacuum of blood drawing or too fine a needle gauge)
- delay in the processing of the blood specimen
- abnormally high numbers of platelets, leukocytes, or erythrocytes (such as myeloproliferative disorders)
- familial causes

Measuring an arterial blood gas will give a quick and accurate measure of true serum potassium. For obtaining a lab sample, using a lithium heparin tube, requesting a slow spin (on the lab centrifuge) and walking the sample to the lab should ensure an accurate result.

Next question >

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Hyperkalaemia

Plasma potassium levels are regulated by a number of factors including aldosterone, acid-base balance and insulin levels. Metabolic acidosis is associated with hyperkalaemia as hydrogen and potassium ions compete with each other for exchange with sodium ions across cell membranes and in the distal tubule. ECG changes seen in hyperkalaemia include tall-tented T waves, small P waves, widened QRS leading to a sinusoidal pattern and asystole

Causes of hyperkalaemia:

- acute kidney injury
- drugs*: potassium sparing diuretics, ACE inhibitors, angiotensin 2 receptor blockers, spironolactone, ciclosporin, heparin**
- metabolic acidosis
- Addison's
- rhabdomyolysis
- massive blood transfusion

Foods that are high in potassium:

- salt substitutes (i.e. Contain potassium rather than sodium)
- bananas, oranges, kiwi fruit, avocado, spinach, tomatoes

*beta-blockers interfere with potassium transport into cells and can potentially cause hyperkalaemia in renal failure patients - remember beta-agonists, e.g. Salbutamol, are sometimes used as emergency treatment

**both unfractionated and low-molecular weight heparin can cause hyperkalaemia. This is thought to be caused by inhibition of aldosterone secretion

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National Kidney Foundation/ British Dietetic Association

[Renal Diet](#)

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Next question >

Renin

Renin is secreted by juxtaglomerular cells and hydrolyses angiotensinogen to produce angiotensin I

Factors stimulating renin secretion

- hypotension causing reduced renal perfusion
- hyponatraemia
- sympathetic nerve stimulation
- catecholamines
- erect posture

Factors reducing renin secretion

- drugs: beta-blockers, NSAIDs

Next question >

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Renin-angiotensin-aldosterone system



Adrenal cortex (mnemonic **GFR - ACD**)

- zona **g**lomerulosa (on outside): mineralocorticoids, mainly **a**ldosterone
- zona **f**asciculata (middle): glucocorticoids, mainly **c**ortisol
- zona **r**eticularis (on inside): androgens, mainly **d**ehydroepiandrosterone (DHEA)

Image sourced from Wikipedia

Renin

- an enzyme that is **released by the renal juxtaglomerular cells in response to reduced renal perfusion**
- other factors that stimulate renin secretion include hyponatraemia, sympathetic nerve stimulation
- hydrolyses angiotensinogen to form angiotensin I

Angiotensin II

- angiotensin-converting enzyme (ACE) in the lungs converts angiotensin I → angiotensin II
- angiotensin II has a wide variety of actions:
- causes **vasoconstriction of vascular smooth muscle** leading to raised blood pressure and **vasoconstriction of efferent arteriole of the glomerulus** → increased filtration fraction (FF) to preserve GFR. Remember that $FF = GFR / \text{renal plasma flow}$
- **stimulates thirst** (via the hypothalamus)
- **stimulates aldosterone and ADH release**
- **increases proximal tubule Na^+/H^+ activity**

Aldosterone

- released by the zona glomerulosa in response to raised **angiotensin II, potassium, and ACTH levels**
- **causes retention of Na^+** in exchange for K^+/H^+ in distal tubule

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Question 7

Which one of the

Rocker bottom

Low-set ears

Webbed neck

Sensory deficit

Seizures

Small, firm test

551 facts found

Score for this

2 in a row correct

Key facts from

Dehydroepiandrosterone

Aldosterone

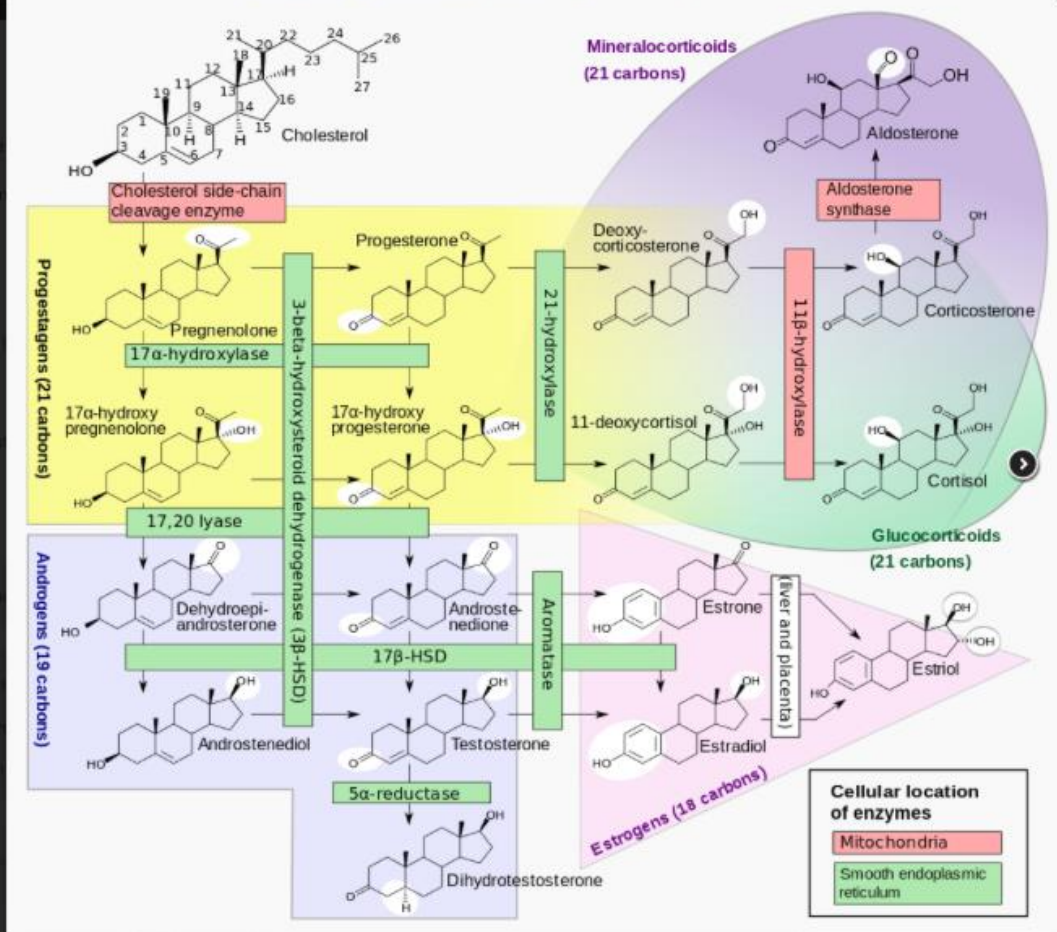
Cortisol

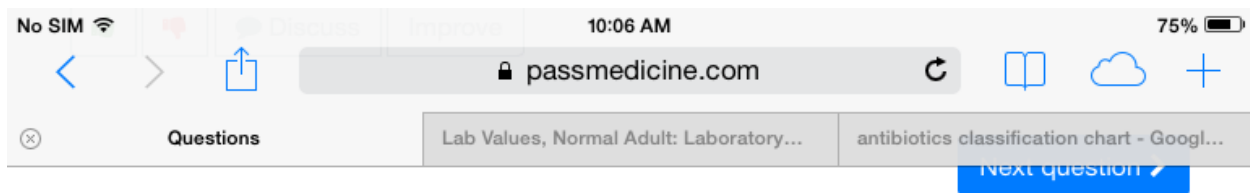
Cortisol

Cortisol

Aldosterone

All contents of





SIADH: causes

The syndrome of inappropriate ADH secretion (SIADH) is characterised by hyponatraemia secondary to the dilutional effects of excessive water retention.

Causes of SIADH

Category	Examples
Malignancy	• small cell lung cancer • also: pancreas, prostate
Neurological	• stroke • subarachnoid haemorrhage • subdural haemorrhage • meningitis/encephalitis/abscess
Infections	• tuberculosis • pneumonia
Drugs	• sulfonylureas* • SSRIs, tricyclics • carbamazepine • vincristine • cyclophosphamide
Other causes	• positive end-expiratory pressure (PEEP) • porphyrias

Management

- correction must be done slowly to avoid precipitating central pontine myelinolysis

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Questions

Lab Values, Normal Adult: Laboratory...

antibiotics classification chart - Googl...

Neurological	- stroke - subarachnoid haemorrhage - subdural haemorrhage - meningitis/encephalitis/abscess
Infections	- tuberculosis - pneumonia
Drugs	- sulfonylureas* - SSRIs, tricyclics - carbamazepine - vincristine - cyclophosphamide
Other causes	- positive end-expiratory pressure (PEEP) - porphyrias

Management

- correction must be done slowly to avoid precipitating central pontine myelinolysis
- fluid restriction
- demeclocycline: reduces the responsiveness of the collecting tubule cells to ADH
- ADH (vasopressin) receptor antagonists have been developed

*the BNF states this has been reported with glimepiride and glipizide.

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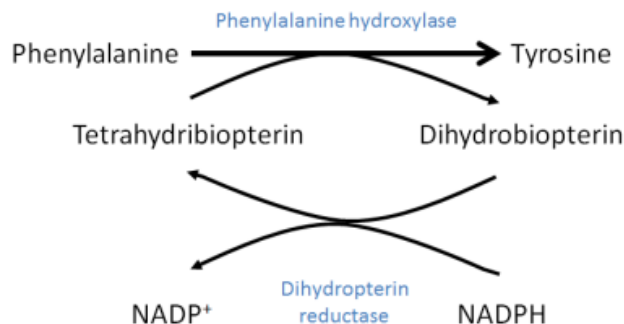
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Phenylketonuria

Phenylketonuria (PKU) is an autosomal recessive condition caused by a disorder of phenylalanine metabolism. This is usually due to defect in phenylalanine hydroxylase, an enzyme which converts phenylalanine to tyrosine. In a small number of cases the underlying defect is a deficiency of the tetrahydrobiopterin-deficient cofactor, e.g. secondary to defective dihydrobiopterin reductase. High levels of phenylalanine lead to problems such as learning difficulties and seizures. The gene for phenylalanine hydroxylase is located on chromosome 12. The incidence of PKU is around 1 in 10,000 live births.



Features

- usually presents by 6 months e.g. with developmental delay
- child classically has fair hair and blue eyes
- learning difficulties
- seizures, typically infantile spasms
- eczema
- 'musty' odour to urine and sweat*

Diagnosis

- Guthrie test: the 'heel-prick' test done at 5-9 days of life - also looks for other biochemical disorders such as hypothyroidism
- hyperphenylalaninaemia
- phenylpyruvic acid in urine

Management

- poor evidence base to suggest strict diet prevents learning disabilities
- dietary restrictions are however important during pregnancy as genetically normal fetuses may be affected by high maternal phenylalanine levels

*secondary to phenylacetate, a phenylketone



Alkaptonuria



Question

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Alkaptonuria (ochronosis) is a rare autosomal recessive disorder of phenylalanine and tyrosine metabolism caused by a lack of the enzyme homogentisic dioxygenase (HGD) which results in a build-up of toxic homogentisic acid. The kidneys filter the homogentisic acid (hence black urine) but eventually it accumulates in cartilage and other tissues.

Alkaptonuria is generally a benign and often asymptomatic condition. Possible features include:

- pigmented sclera
- urine turns black if left exposed to the air
- intervertebral disc calcification may result in back pain
- renal stones

Treatment

- high-dose vitamin C
- dietary restriction of phenylalanine and tyrosine



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Multi-level intervertebral disc calcification with disc space narrowing

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Calcium metabolism

The two hormones which primarily control calcium metabolism are:

- parathyroid hormone (PTH)
- 1,25-dihydroxycholecalciferol (calcitriol, the active form of vitamin D)

Other hormones include

- calcitonin: secreted from the parafollicular cells (C-cells) of the thyroid gland
- thyroxine
- growth hormone

Actions of parathyroid hormone

- increases plasma calcium, decreases plasma phosphate
- increases renal tubular reabsorption of calcium
- increases osteoclastic activity*
- increases renal conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol
- decreases renal phosphate reabsorption

Actions of 1,25-dihydroxycholecalciferol

- increases plasma calcium and plasma phosphate
- increases renal tubular reabsorption and gut absorption of calcium
- increases osteoclastic activity
- increases renal phosphate reabsorption

*this is actually via an indirect mechanism as osteoclasts don't have PTH receptors

Next question >

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Next question >

Hypocalcaemia: features

As extracellular calcium concentrations are important for muscle and nerve function many of the features seen in hypocalcaemia seen a result of neuromuscular excitability

Features

- tetany: muscle twitching, cramping and spasm
- perioral paraesthesia
- if chronic: depression, cataracts
- ECG: prolonged QT interval

Trousseau's sign

- carpal spasm if the brachial artery occluded by inflating the blood pressure cuff and maintaining pressure above systolic
- wrist flexion and fingers drawn together
- seen in around 95% of patients with hypocalcaemia and around 1% of normocalcaemic people

Chvostek's sign

- tapping over parotid causes facial muscles to twitch
- seen in around 70% of patients with hypocalcaemia and around 10% of normocalcaemic people

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Questions

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Lab Values, Normal Adult:...

Discuss (5)

Improve

Next question >

Hypocalcaemia: causes and management

The clinical history combined with parathyroid hormone levels will reveal the cause of hypocalcaemia in the majority of cases

Causes

- vitamin D deficiency (osteomalacia)
- chronic renal failure
- hypoparathyroidism (e.g. post thyroid/parathyroid surgery)
- pseudohypoparathyroidism (target cells insensitive to PTH)
- rhabdomyolysis (initial stages)
- magnesium deficiency (due to end organ PTH resistance)
- massive blood transfusion

Acute pancreatitis may also cause hypocalcaemia. Contamination of blood samples with EDTA may also give falsely low calcium levels

Management

- acute management of severe hypocalcaemia is with intravenous replacement. The preferred method is with intravenous calcium gluconate, 10ml of 10% solution over 10 minutes
- intravenous calcium chloride is more likely to cause local irritation
- ECG monitoring is recommended
- further management depends on the underlying cause

Next question >

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Refeeding syndrome causes hypophosphataemia

This patient is at risk of refeeding syndrome, which can lead to profound hypophosphataemia



[Discuss \(1\)](#)
[Improve](#)

[Next question >](#)

Hypophosphataemia

Causes

- alcohol excess
- acute liver failure
- diabetic ketoacidosis
- refeeding syndrome
- primary hyperparathyroidism
- osteomalacia

Consequences

- red blood cell haemolysis
- white blood cell and platelet dysfunction
- muscle weakness and rhabdomyolysis
- central nervous system dysfunction

[Next question >](#)

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Next question >

Hypercalcaemia: management

The initial management of hypercalcaemia is rehydration with normal saline, typically 3-4 litres/day. Following rehydration bisphosphonates may be used. They typically take 2-3 days to work with maximal effect being seen at 7 days

Other options include:

- calcitonin - quicker effect than bisphosphonates
- steroids in sarcoidosis

Loop diuretics such as furosemide are sometimes used in hypercalcaemia, particularly in patients who cannot tolerate aggressive fluid rehydration. However, they should be used with caution as they may worsen electrolyte derangement and volume depletion.

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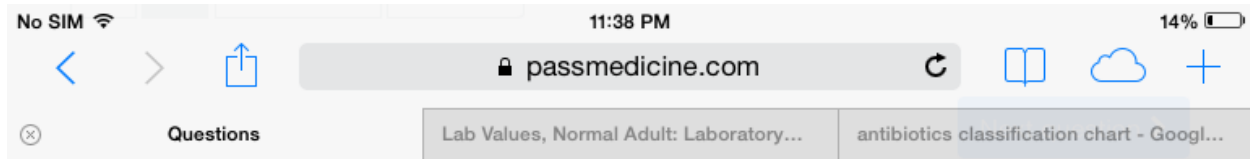
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Renal anatomy

Each kidney is about 11cm long, 5cm wide and 3cm thick. They are located in a deep gutter alongside the projecting vertebral bodies, on the anterior surface of psoas major. In most cases the left kidney lies approximately 1.5cm higher than the right. The upper pole of both kidneys approximates with the 11th rib (beware pneumothorax during nephrectomy). On the left hand side the hilum is located at the L1 vertebral level and the right kidney at level L1-2. The lower border of the kidneys is usually alongside L3.

Relations

The tables below show the anatomical relations of the kidneys:

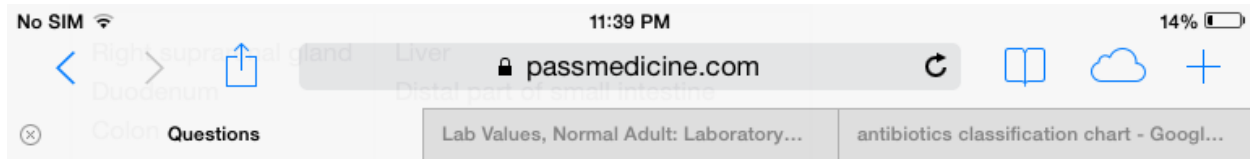
Relations	Right Kidney	Left Kidney
Posterior	Quadratus lumborum, diaphragm, psoas major, transversus abdominis	Quadratus lumborum, diaphragm, psoas major, transversus abdominis
Anterior	Hepatic flexure of colon	Stomach, Pancreatic tail
Superior	Liver, adrenal gland	Spleen, adrenal gland

If we consider relations according to whether they are in direct contact or whether there is peritoneum in-between:

Right kidney

Direct contact	Layer of peritoneum in-between
Right suprarenal gland Duodenum Colon	Liver Distal part of small intestine

Left kidney



Left kidney

Direct contact	Layer of peritoneum in-between
Left suprarenal gland	Stomach
Pancreas	Spleen
Colon	Distal part of small intestine

Fascial covering

Each kidney and suprarenal gland is enclosed within a common layer of investing fascia, derived from the transversalis fascia. It is divided into anterior and posterior layers (Gerotas fascia).

Renal structure

Kidneys are surrounded by an outer cortex and an inner medulla which usually contains between 6 and 10 pyramidal structures. The papilla marks the innermost apex of these. They terminate at the renal pelvis, into the ureter.

Lying in a hollow within the kidney is the renal sinus. This contains:

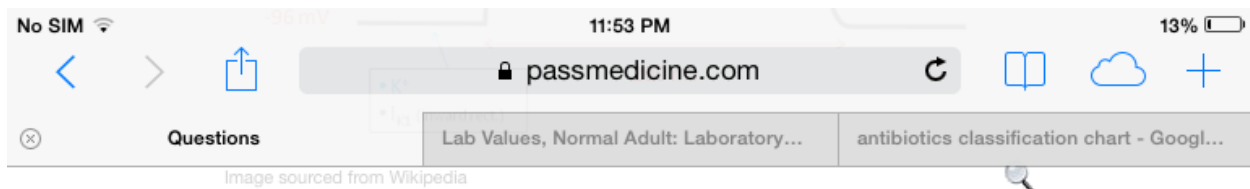
- 1. Branches of the renal artery
- 2. Tributaries of the renal vein
- 3. Major and minor calyces's
- 4. Fat

Structures at the renal hilum

The renal vein lies most anteriorly, then renal artery (it is an end artery) and the ureter lies most posterior.

Next question >

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Phase	Description	Mechanism
0	Rapid depolarisation	Rapid sodium influx These channels automatically deactivate after a few ms
1	Early repolarisation	Efflux of potassium
2	Plateau	Slow influx of calcium
3	Final repolarisation	Efflux of potassium
4	Restoration of ionic concentrations	Resting potential is restored by Na^+/K^+ ATPase There is slow entry of Na^+ into the cell decreasing the potential difference until the threshold potential is reached, triggering a new action potential

NB cardiac muscle remains contracted 10-15 times longer than skeletal muscle

Conduction velocity

Site	Speed
Atrial conduction	Spreads along ordinary atrial myocardial fibres at 1 m/sec
AV node conduction	0.05 m/sec
Ventricular conduction	Purkinje fibres are of large diameter and achieve velocities of 2-4 m/sec (this allows a rapid and coordinated contraction of the ventricles)

Next question

Next question >

Antidiuretic hormone

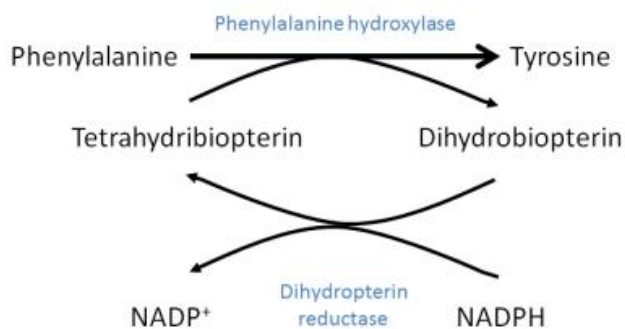
Antidiuretic hormone (ADH) is secreted from the posterior pituitary gland. It promotes water reabsorption in the collecting ducts of the kidneys by the insertion of aquaporin-2 channels.

	Notes	Further detail
Source	Synthesized in the supraoptic nuclei of the hypothalamus, released by the pituitary pituitary	
Function	Conserves body water	Promotes water reabsorption in the collecting ducts of the kidneys by the insertion of aquaporin-2 channels
Regulation	Increases secretion • extracellular fluid osmolality increase • volume decrease • pressure decrease • angiotensin II Decreases secretion • extracellular fluid osmolality decrease • volume increase • temperature decrease	Diabetes insipidus (DI) is a condition characterised by either a deficiency of antidiuretic hormone, ADH, (cranial DI) or an insensitivity to antidiuretic hormone (nephrogenic DI) Cranial DI can be treated by desmopressin, an analog of ADH

Next question >

Phenylketonuria

Phenylketonuria (PKU) is an autosomal recessive condition caused by a disorder of phenylalanine metabolism. This is usually due to defect in phenylalanine hydroxylase, an enzyme which converts phenylalanine to tyrosine. In a small number of cases the underlying defect is a deficiency of the tetrahydrobiopterin-deficient cofactor, e.g. secondary to defective dihydrobiopterin reductase. High levels of phenylalanine lead to problems such as learning difficulties and seizures. The gene for phenylalanine hydroxylase is located on chromosome 12. The incidence of PKU is around 1 in 10,000 live births.

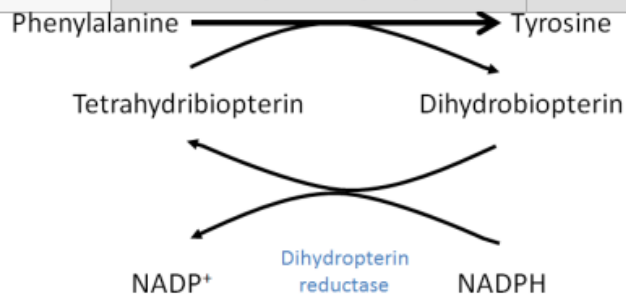


Features

- usually presents by 6 months e.g. with developmental delay
- child classically has fair hair and blue eyes
- learning difficulties
- seizures, typically infantile spasms
- eczema
- 'musty' odour to urine and sweat*

Diagnosis

- Guthrie test: the 'heel-prick' test done at 5-9 days of life - also looks for other biochemical disorders such as hypothyroidism
- hyperphenylalaninaemia
- phenylpyruvic acid in urine



Features

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Diagnosis

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- hyperphenylalaninaemia
- phenylpyruvic acid in urine

Management

- poor evidence base to suggest strict diet prevents learning disabilities
- dietary restrictions are however important during pregnancy as genetically normal fetuses may be affected by high maternal phenylalanine levels

*secondary to phenylacetate, a phenylketone

Next question >

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Renal physiology

Overview

- each nephron is supplied with blood from an afferent arteriole that opens onto the glomerular capillary bed
- blood then flows to an efferent arteriole, supplying the peritubular capillaries and medullary vasa recta
- the kidney receives up to 25% of resting cardiac output

Control of blood flow

- the kidney is able to autoregulate its blood flow between systolic pressures of 80-180mmHg so there is little variation in renal blood flow
- this is achieved by myogenic control of arteriolar tone, both sympathetic input and hormonal signals (e.g. renin) are responsible
- renal cortical blood flow > medullary blood flow (i.e. tubular cells more prone to ischaemia)

Glomerular structure and function

- blood inside the glomerulus has considerable hydrostatic pressure
- the basement membrane has pores that will allow free diffusion of smaller solutes, larger negatively charged molecules such as albumin are unable to cross
- the glomerular filtration rate (GFR) is equal to the concentration of a solute in the urine, times the volume of urine produced per minute, divided by the plasma concentration (assuming that the solute is freely diffused e.g. inulin)
- in clinical practice creatinine is used because it is subjected to very little proximal tubular secretion
- although subject to variability, the typical GFR is 125ml per minute
- glomerular filtration rate = Total volume of plasma per unit time leaving the capillaries and entering the Bowman's capsule
- renal clearance = volume plasma from which a substance is removed per minute by the kidneys

Substances used to measure GFR have the following features:

1. Inert
2. Free filtration from the plasma at the glomerulus (not protein bound)
3. Not absorbed or secreted at the tubules
4. Plasma concentration constant during urine collection

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- 1. Inert
- 2. Free filtration from the plasma at the glomerulus (not protein bound)
- 3. Not absorbed or secreted at the tubules
- 4. Plasma concentration constant during urine collection
- examples: inulin, creatinine

$$\text{GFR} = \frac{\text{urine concentration (mmol/l)} \times \text{urine volume (ml/min)}}{\text{plasma concentration (mmol/l)}}$$

- the clearance of a substance is dependent not only on its diffusivity across the basement membrane but also subsequent tubular secretion and / or reabsorption
- so glucose which is freely filtered across the basement membrane is usually reabsorbed from tubules giving a clearance of zero

Tubular function

- reabsorption and secretion of substances occurs in the tubules
- in the proximal tubule substrates such as glucose, amino acids and phosphate are co-transported with sodium across the semi permeable membrane
- up to two thirds of filtered water is reabsorbed in the proximal tubules
- this will lead to increase in urea concentration in the distal tubule allowing for its increased diffusion
- substances to be secreted into the tubules are taken up from the peritubular blood by tubular cells
- solutes such as para-aminohippuric acid are cleared with a single passage through the kidneys and this is why it is used to measure renal plasma flow. Ions such as calcium and phosphate will have a tubular reabsorption that is influenced by plasma PTH levels
- potassium may be both secreted and reabsorbed and is co-exchanged with sodium

Loop of Henle

- approximately 60 litres of water containing 9000mmol sodium enters the descending limb of the loop of Henle in 24 hours
- loops from the juxtamedullary nephrons run deep into the medulla
- the osmolarity of fluid changes and is greatest at the tip of the papilla
- the thin ascending limb is impermeable to water, but highly permeable to sodium and chloride ions
- this loss means that at the beginning of the thick ascending limb the fluid is hypo osmotic compared with adjacent interstitial fluid
- in the thick ascending limb the reabsorption of sodium and chloride ions occurs by both

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- this loss means that at the beginning of the thick ascending limb the fluid is hypo osmotic compared with adjacent interstitial fluid
- in the thick ascending limb the reabsorption of sodium and chloride ions occurs by both facilitated and passive diffusion pathways
- the loops of Henle are co-located with vasa recta, these will have similar solute compositions to the surrounding extracellular fluid so preventing the diffusion and subsequent removal of this hypertonic fluid
- the energy dependent reabsorption of sodium and chloride in the thick ascending limb helps to maintain this osmotic gradient

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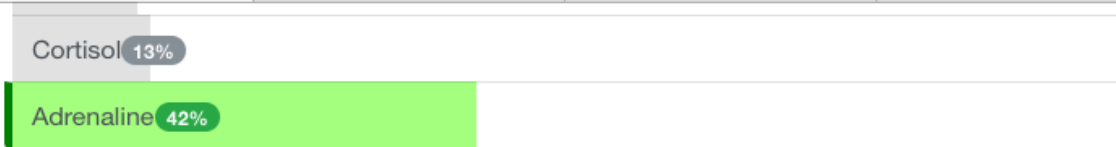
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Adrenal medulla

The adrenal medulla secretes virtually all the adrenaline in the body as well as secreting small amounts of noradrenaline. It essentially represents an enlarged and specialised sympathetic ganglion

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Enzyme-linked immunosorbent assay (ELISA)

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PCR

Polymerase chain reaction (PCR) is a molecular genetic investigation technique. The main advantage of PCR is its sensitivity: only one strand of sample DNA is needed to detect a particular DNA sequence. It now has many uses including prenatal diagnosis, detection of mutated oncogenes and diagnosis of infections. PCR is also extensively used in forensics. Prior to the procedure it is necessary to have two DNA oligonucleotide primers. These are complimentary to specific DNA sequences at either end of the target DNA

Initial prep

- sample of DNA is added to test tube along with two DNA primers
- a thermostable DNA polymerase (Taq) is added

The following cycle then takes place

- mixture is heated to almost boiling point causing denaturing (uncoiling) of DNA
- mixture is the allowed to cool: complimentary strands of DNA pair up, as there is an excess of the primer sequences they pair with DNA preferentially

The above cycle is then repeated, with the amount of DNA doubling each time

Reverse transcriptase PCR

- used to amplify RNA
- RNA is converted to DNA by reverse transcriptase
- gene expression in the form of mRNA (rather than the actually DNA sequence) can therefore be analyzed

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Cell surface proteins

The table below shows the most common cell surface proteins associated with particular cell types:

Type of cell	Cell surface markers
Haematopoietic stem cells	CD34
Helper T cell	CD4, TCR, CD3, CD28
Cytotoxic T cell	CD8, TCR, CD3, CD28
Regulatory T cell	CD4, CD25, TCR, CD3, CD28
B cell	CD19, CD20, CD40, MHC II, B7
Macrophage	CD14, CD40, MHC II, B7
Natural killer cell	CD16, CD56

The table below lists the major clusters of differentiation (CD) molecules and describes their function.

Cluster of differentiation	Function
CD1	MHC molecule that presents lipid molecules
CD2	Found on thymocytes, T cells, and some natural killer cells that acts as a ligand for CD58 and CD59 and is involved in signal transduction and cell adhesion
CD3	The signalling component of the T cell receptor (TCR) complex
CD4	Found on helper T cells. Co-receptor for MHC class II Used by HIV to enter T cells
CD5	Found in the majority of mantle cell lymphomas
CD8	Found on cytotoxic T cells. Co-receptor for MHC class I Found on a subset of myeloid dendritic cells

their function.

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CD14	Cell surface marker for macrophages
CD15	Expressed on Reed-Sternberg cells (along with CD30)
CD16	Bind to the Fc portion of IgG antibodies
CD21	Receptor for Epstein-Barr virus
CD28	Interacts with B7 on antigen presenting cell as costimulation signal
CD45	Protein tyrosine phosphatase present on all leucocytes
CD56	Unique marker for natural killer cells
CD95	Acts as the FAS receptor, involved in apoptosis

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Membrane receptors

There are four main types of membrane receptor: ligand-gated ion channels, tyrosine kinase receptors, guanylate cyclase receptors and G protein-coupled receptors

Ligand-gated ion channel receptors

- generally mediate fast responses
- e.g. nicotinic acetylcholine, GABA-A & GABA-C, glutamate receptors

Tyrosine kinase receptors

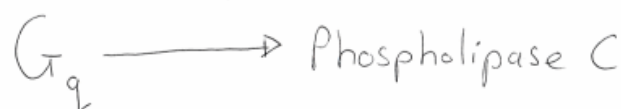
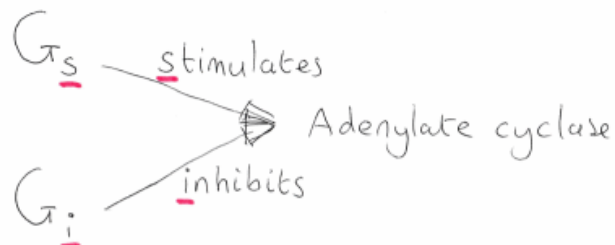
- intrinsic tyrosine kinase: insulin, insulin-like growth factor (IGF), epidermal growth factor (EGF)
- receptor-associated tyrosine kinase: growth hormone, prolactin, interferon, interleukin

Guanylate cyclase receptors

- contain intrinsic enzyme activity
- e.g. atrial natriuretic factor, brain natriuretic peptide

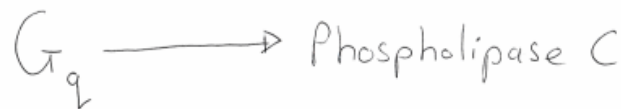
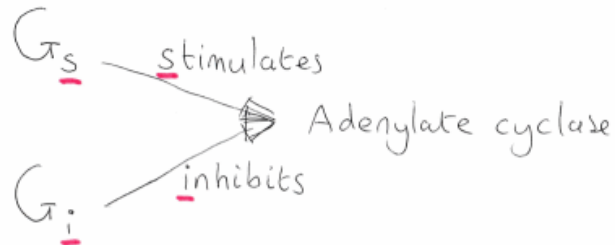
G protein-coupled receptors

- generally mediate slow transmission and affect metabolic processes
- activated by a wide variety of extracellular signals e.g. Peptide hormones, biogenic amines, lipophilic hormones, light
- 7-helix membrane-spanning domains
- consist of 3 main subunits: alpha, beta and gamma
- the alpha subunit is linked to GDP. Ligand binding causes conformational changes to receptor, GDP is phosphorylated to GTP, and the alpha subunit is activated
- G proteins are named according to the alpha subunit (G_s , G_i , G_q)



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	G_s	G_i	G_q
Mechanism	Stimulates adenylate cyclase → increases cAMP → activates protein kinase A	Inhibits adenylate cyclase → decreases cAMP → inhibits protein kinase A	Activates phospholipase C → splits PIP_2 to IP_3 & DAG → activates protein kinase C
Examples	- Beta-1 receptors (epinephrine, norepinephrine, dobutamine) - Beta-2 receptors (epinephrine, salbutamol) - H2 receptors (histamine) - D1 receptors (dopamine) - V2 receptors (vasopressin) - Receptors for ACTH, LH, FSH, glucagon, PTH, calcitonin, prostaglandins	- M2 receptors (acetylcholine) - Alpha-2 receptors (epinephrine, norepinephrine) - D2 receptors (dopamine) - GABA-B receptor	- Alpha-1 receptors (epinephrine, norepinephrine) - H1 receptors (histamine) - V1 receptors (vasopressin) - M1, M3 receptors (acetylcholine)

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antibiotics classification chart - Googl...

Cell organelles

The table below summarises the main functions of the major cell organelles:

Organelle/macromolecule	Main function
Endoplasmic reticulum	Rough endoplasmic reticulum - translation and folding of new proteins - manufacture of lysosomal enzymes - site of N-linked glycosylation - examples of cells with extensive RER include pancreatic cells, goblet cells, plasma cells Smooth endoplasmic reticulum - steroid, lipid synthesis - examples of cells with extensive SER include those of the adrenal cortex, hepatocytes, testes, ovaries
Golgi apparatus	Modifies, sorts, and packages these molecules that are destined for cell secretion Site of O-linked glycosylation
Mitochondrion	Aerobic respiration. Contains mitochondrial genome as circular DNA
Nucleus	DNA maintenance and RNA transcription
Lysosome	Breakdown of large molecules such as proteins and polysaccharides
Nucleolus	Ribosome production
Ribosome	Translation of RNA into proteins
Peroxisome	Catabolism of very long chain fatty acids and amino acids Results in the formation of hydrogen peroxide
Proteasome	Along with the lysosome pathway involved in degradation of protein molecules that have been tagged with ubiquitin

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Complement deficiencies

Complement is a series of proteins that circulate in plasma and are involved in the inflammatory and immune reaction of the body. Complement proteins are involved in chemotaxis, cell lysis and opsonisation

C1 inhibitor (C1-INH) protein deficiency

- causes hereditary angioedema
- C1-INH is a multifunctional serine protease inhibitor
- probable mechanism is uncontrolled release of bradykinin resulting in oedema of tissues

C1q, C1rs, C2, C4 deficiency (classical pathway components)

- predisposes to immune complex disease
- e.g. SLE, Henoch-Schonlein Purpura

C3 deficiency

- causes recurrent bacterial infections

C5 deficiency

- predisposes to Leiner disease
- recurrent diarrhoea, wasting and seborrhoeic dermatitis

C5-9 deficiency

- encodes the membrane attack complex (MAC)
- particularly prone to *Neisseria meningitidis* infection

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IL-4, IL-5, IL-6, IL-10, IL-13 15%



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T-Helper cells

There are two major subsets of T-Helper cells:

Th1

- involved in the cell mediated response and delayed (type IV) hypersensitivity
- secrete IFN-gamma, IL-2, IL-3

Th2

- involved in mediating humoral (antibody) immunity
- e.g. stimulating production of IgE in asthma
- secrete IL-4, IL-5, IL-6, IL-10, IL-13

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Cytokines

Interleukins

Cytokine	Main sources	Functions
IL-1	Macrophages	Acute inflammation Induces fever
IL-2	Th1 cells	Stimulates growth and differentiation of T cell response
IL-3	Activated T helper cells	Stimulates differentiation and proliferation of myeloid progenitor cells
IL-4	Th2 cells	Stimulates proliferation and differentiation of B cells
IL-5	Th2 cells	Stimulate production of eosinophils
IL-6	Macrophages, Th2 cells	Stimulates differentiation of B cells Induces fever
IL-8	Macrophages	Neutrophil chemotaxis
IL-10 Th2 cells	Inhibits Th1 cytokine production Also known as human cytokine synthesis inhibitory factor and is an 'anti-inflammatory' cytokine	
IL-12	Dendritic cells, macrophages, B cells	Activates NK cells and stimulates differentiation of naive T cells into Th1 cells

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IL-6	Macrophages, Th2 cells	Stimulates differentiation of B cells Induces fever
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Other cytokines

Cytokine	Main sources	Functions
Tumour necrosis factor- α	Macrophages	Induces fever Neutrophil chemotaxis
Interferon- γ	Th1 cells	Activates macrophages

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IL-1

Interleukin 1 (IL-1) is a key mediator of the immune response. It is secreted mainly by macrophages and monocytes and acts as a costimulator of T cell and B cell proliferation.

Other effects include increasing the expression of adhesion molecules on the endothelium. By stimulating the release by the endothelium of vasoactive factors such as PAF, nitric oxide and prostacyclin it also causes vasodilation and increases vascular permeability. It is therefore one of the mediators of shock in sepsis. Along with IL-6 and TNF, it acts on the hypothalamus causing pyrexia.

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Leukotrienes

Function

- mediators of inflammation and allergic reactions
- cause bronchoconstriction, mucous production
- increase vascular permeability, attract leukocytes
- leukotriene D4 has been identified as the SRS-A (slow reacting substance of anaphylaxis)

Production

- secreted by leukocytes
- formed from arachidonic acid by action of lipoxygenase
- it is thought that the NSAID induced bronchospasm in asthmatics is secondary to the express production of leukotrienes due to the inhibition of prostaglandin synthetase

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Interferon

Interferons (IFN) are cytokines released by the body in response to viral infections and neoplasia. They are classified according to cellular origin and the type of receptor they bind to. IFN-alpha and IFN-beta bind to type 1 receptors whilst IFN-gamma binds only to type 2 receptors.

IFN-alpha

- produced by leucocytes
- antiviral action
- useful in hepatitis B & C, Kaposi's sarcoma, metastatic renal cell cancer, hairy cell leukaemia
- adverse effects include flu-like symptoms and depression

IFN-beta

- produced by fibroblasts
- antiviral action
- reduces the frequency of exacerbations in patients with relapsing-remitting MS

IFN-gamma

- produced by T lymphocytes & NK cells
- weaker antiviral action, more of a role in immunomodulation particularly macrophage activation
- may be useful in chronic granulomatous disease and osteopetrosis

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Immunoglobulins

The table below summarises the characteristics of the 5 types of immunoglobulin found in the body:

Type	Frequency	Shape	Notes
IgG	75%	Monomer	- Enhance phagocytosis of bacteria and viruses - Fixes complement and passes to the fetal circulation - Most abundant isotype in blood serum
IgA	15%	Monomer/ dimer	- IgA is the predominant immunoglobulin found in breast milk. It is also found in the secretions of digestive, respiratory and urogenital tracts and systems - Provides localized protection on mucous membranes - Most commonly produced immunoglobulin in the body (but blood serum concentrations lower than IgG .) - Transported across the interior of the cell via transcytosis
IgM	10%	Pentamer	- First immunoglobulins to be secreted in response to an infection - Fixes complement but does not pass to the fetal circulation - Anti-A, B blood antibodies (note how they cannot pass to the fetal circulation, which could of course result in haemolysis) - Pentamer when secreted
IgD	1%	Monomer	- Role in immune system largely unknown - Involved in activation of B cells
IgE	0.1%	Monomer	- Mediates type 1 hypersensitivity reactions - Binds to Fc receptors found on the surface of mast cells and basophils - Provides immunity to parasites such as helminths

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Immune system cells: adaptive immune response

The following cells are mostly involved in the adaptive immune response:

Cell type	Functions and properties
Helper T cells	Involved in the cell-mediated immune response Recognises antigens presented by MHC class II molecules Expresses CD4 Also expresses CD3, TCR & CD28 Major source of IL-2 Mediates acute and chronic organ rejection
Cytotoxic T cells	Involved in the cell-mediated immune response Recognises antigens presented by MHC class I molecules Induce apoptosis in virally infected and tumour cells Expresses CD8 Also expresses CD3, TCR Mediates acute and chronic organ rejection
B cells	Major cell of the humoral immune response Acts as an antigen presenting cell Mediates hyperacute organ rejection
Plasma cells	Differentiated from B cells Produces large amounts of antibody specific to a particular antigen

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Immune system cells: innate immune response

The following cells are mostly involved in the innate immune response:

Cell type	Functions and properties
Neutrophil	Primary phagocytic cell in acute inflammation Granules contain myeloperoxidase and lysozyme Most common type of white blood cell Multi-lobed nucleus
Basophil	Releases histamine during allergic response Granules contain histamine and heparin Expresses IgE receptors on the cell surface Bi-lobed nucleus
Mast cell	Present in tissues and are similar in function to basophils but derived from different cell lines Releases histamine during allergic response Granules contain histamine and heparin Expresses IgE receptors on the cell surface
Eosinophil	Defends against protozoan and helminthic infections Bi-lobed nucleus
Monocyte	Differentiates into macrophages Kidney shaped nucleus
Macrophage	Involved in phagocytosis of cellular debris and pathogens Acts as an antigen presenting cell Major source of IL-1
Natural killer cell	Induce apoptosis in virally infected and tumour cells
Dendritic cell	Acts as an antigen presenting cell

Second messengers

Overview

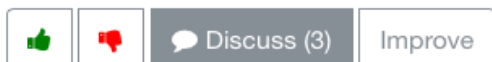
- many different types
- allow amplification of external stimulus

	cAMP system	Phosphoinositol system	cGMP system	Tyrosine kinase system
Ligand: Neurotransmitters (Receptor)	Epinephrine (α_2 , β_1 , β_2) Acetylcholine (M2)	Epinephrine (α_1) Acetylcholine (M1, M3)	-	-
Ligand: Hormones	ACTH, ADH, calcitonin, FSH, glucagon, hCG, LH, MSH, PTH, TSH, GHRH*	angiotensin II, GnRH, GHRH*, Oxytocin, TRH	ANP, Nitric oxide	insulin, growth hormone, IGF, PDGF
Primary effector	Adenylyl cyclase	Phospholipase C	Guanylate cyclase	Receptor tyrosine kinase
Secondary messenger	cAMP (cyclic adenosine monophosphate)	IP3 (inositol 1,4,5 trisphosphate) and DAG (Diacylglycerol)	cGMP	Protein phosphatase

*the cAMP pathway is the most important

Next question >

The nurse is likely to suffer from latex-fruit syndrome.



Next question >

Latex allergy

Sensitivity to latex may cause a number of problems:

- type I hypersensitivity (anaphylaxis)
- type IV hypersensitivity (allergic contact dermatitis)
- irritant contact dermatitis

Latex allergy is more common in children with myelomeningocele spina bifida.

Latex-fruit syndrome

It is recognised that many people who are allergic to latex are also allergic to fruits, particularly banana, pineapple, avocado, chestnut, kiwi fruit, mango, passion fruit and strawberry.

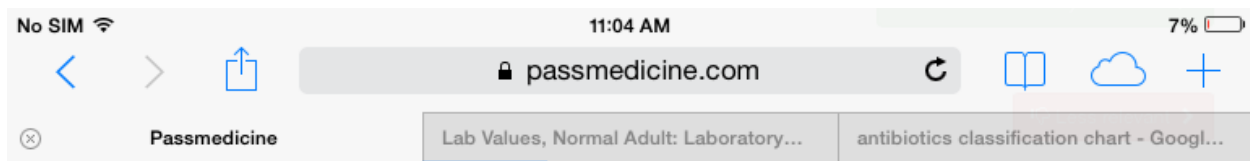
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Cell cycle

The cell cycle is regulated by proteins called cyclins which in turn control cyclin-dependent kinase (CDK) enzymes.

Phase	Notes	Regulatory proteins
G ₀	'resting' phase - quiescent cells such as hepatocytes and more permanently resting cells such as neurons	
G ₁	Gap 1, cells increase in size - determines length of cell cycle - under influence of p53	Cyclin D / CDK4, Cyclin D / CDK6 and Cyclin E / CDK2: regulates transition from G ₁ to S phase
S	Synthesis of DNA, RNA and histone - centrosome duplication	Cyclin A / CDK2: active in S phase
G ₂	Gap 2, cells continue to increase in size	Cyclin B / CDK1: regulates transition from G ₂ to M phase
M	Mitosis - cell division - the shortest phase of the cell cycle	

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Cell division

There are two types of cell division; mitosis and meiosis.

The table below demonstrates the key differences:

Mitosis	Meiosis
Occurs in somatic cells	Occurs in gametes
Results in 2 diploid daughter cells	Results in 4 haploid daughter cells
Daughter cells are genetically identical to parent cell	Daughter cells contain one homologue of each chromosome pair and are therefore genetically different

Remember:

- somatic cells have 22 pairs of autosomes and 1 pair of sex chromosomes, i.e. 46XY or 46XX
- cells with a normal chromosome complement are known as diploid cells
- gametes (ova or spermatozoa) have a single copy of each chromosome and are known as haploid cells

Mitosis

Mitosis occurs during the M phase of the cell cycle. It describes the process in which somatic cells divide and replicate producing genetically identical diploid daughter cells. This allows tissue to grow and renew itself.

During the S phase of the cell cycle the cell prepares itself for division by duplicating the chromosomes. The table below shows the phases of mitosis itself:

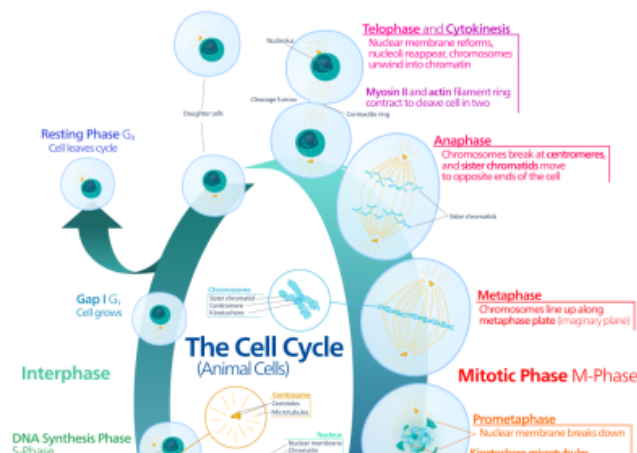
Prophase	Chromatin in the nucleus condenses
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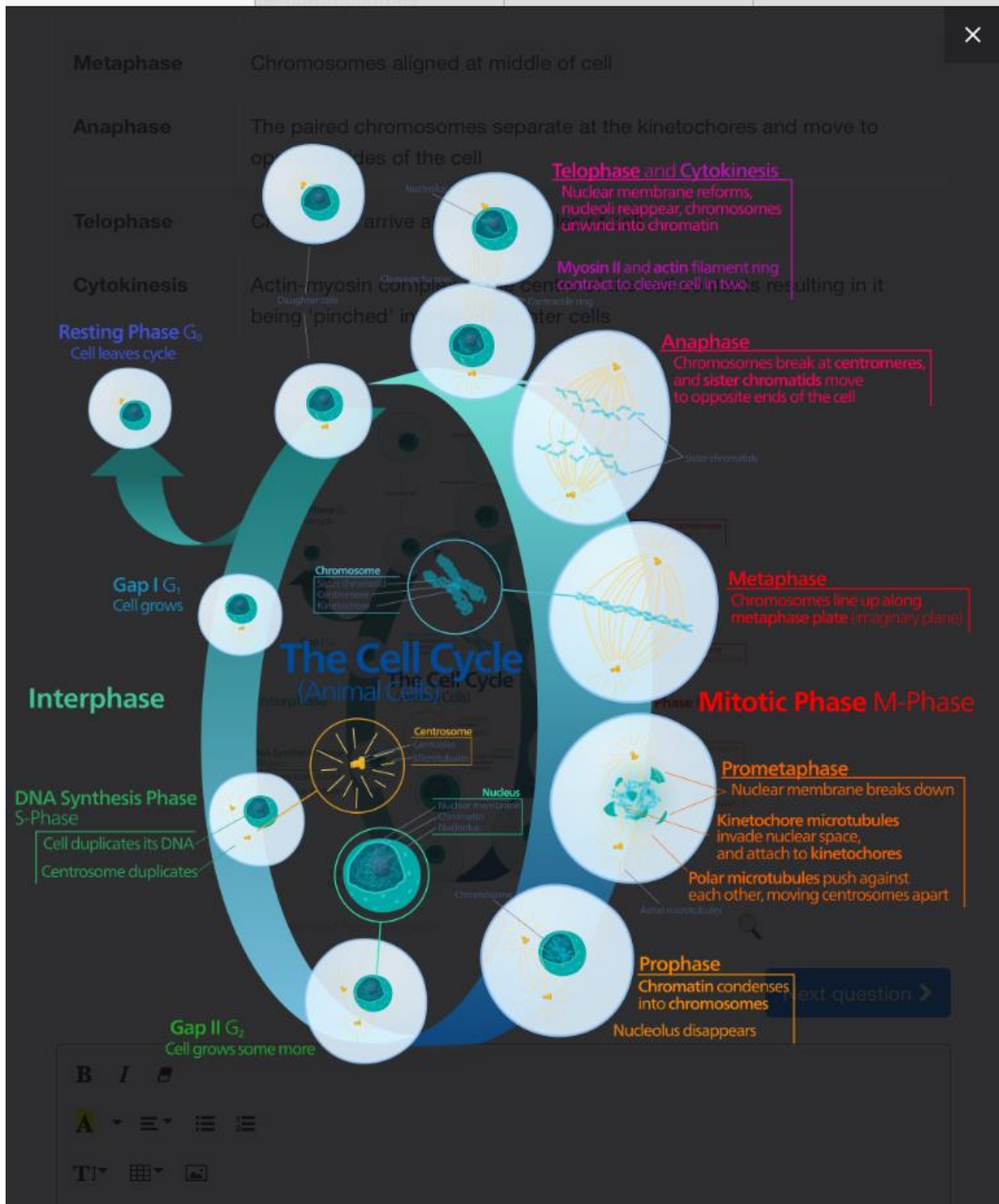
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Prophase	Chromatin in the nucleus condenses
Prometaphase	Nuclear membrane breaks down allowing the microtubules to attach to the chromosomes
Metaphase	Chromosomes aligned at middle of cell
Anaphase	The paired chromosomes separate at the kinetochores and move to opposite sides of the cell
Telophase	Chromatids arrive at opposite poles of cell
Cytokinesis	Actin-myosin complex in the centre of the cell contracts resulting in it being 'pinched' into two daughter cells





Collagen

Collagen is the main structural protein found in connective tissue and is the most common protein found in the body.

Whilst over 20 types of collagen have been identified there are 4-5 which are considered the most important:

Collagen type	Notes	Associated conditions
I	Bone, skin, tendon	Osteogenesis imperfecta
II	Hyaline cartilage, vitreous humour	
III	Reticular fibre, granulation tissue	Vascular variant of Ehlers-Danlos syndrome
IV	Basal lamina, lens, basement membrane	Alport syndrome, Goodpasture's syndrome
V	Most interstitial tissue, placental tissue	Classical variant of Ehlers-Danlos syndrome

Structure

- Composed of 3 polypeptide strands that are woven into a helix, usually a combination of glycine with either proline or hydroxyproline plus another amino acid
- Numerous hydrogen bonds exist within molecule to provide additional strength
- Many subtypes but commonest subtype is I (90% of bodily collagen), tissues with increased levels of flexibility have increased levels of type III collagen
- Vitamin C is important in establishing cross-links
- Synthesised by fibroblasts

Collagen diseases

Collagen diseases

Disorders of collagen range from relatively common, acquired defects (typically aging), through to rarer congenital disorders. The latter are exemplified by conditions such as osteogenesis imperfecta and Ehlers Danlos syndromes.

Osteogenesis imperfecta:

- 8 Subtypes
- Defect of type I collagen
- In type I the collagen is normal quality but insufficient quantity
- Type II- poor quantity and quality
- Type III- Collagen poorly formed, normal quantity
- Type IV- Sufficient quantity but poor quality
- Patients have bones which fracture easily, loose joint and multiple other defects depending upon which sub type they suffer from.

Ehlers Danlos:

- Multiple sub types
- Abnormality of types 1 and 3 collagen
- Patients have features of hypermobility.
- Individuals are prone to joint dislocations and pelvic organ prolapse. In addition to many other diseases related to connective tissue defects.

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ⓧ Questions

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Lab Values, Normal Adult:...

Cell surface proteins

The table below shows the most common cell surface proteins associated with particular cell types:

Type of cell	Cell surface markers
Haematopoietic stem cells	CD34
Helper T cell	CD4, TCR, CD3, CD28
Cytotoxic T cell	CD8, TCR, CD3, CD28
Regulatory T cell	CD4, CD25, TCR, CD3, CD28
B cell	CD19, CD20, CD40, MHC II, B7
Macrophage	CD14, CD40, MHC II, B7
Natural killer cell	CD16, CD56

The table below lists the major clusters of differentiation (CD) molecules and describes their function.

Cluster of differentiation	Function
CD1	MHC molecule that presents lipid molecules
CD2	Found on thymocytes, T cells, and some natural killer cells that acts as a ligand for CD58 and CD59 and is involved in signal transduction and cell adhesion
CD3	The signalling component of the T cell receptor (TCR) complex
CD4	Found on helper T cells

Cluster of differentiation	Function
CD1	MHC molecule that presents lipid molecules
CD2	Found on thymocytes, T cells, and some natural killer cells that acts as a ligand for CD58 and CD59 and is involved in signal transduction and cell adhesion
CD3	The signalling component of the T cell receptor (TCR) complex
CD4	Found on helper T cells. Co-receptor for MHC class II Used by HIV to enter T cells
CD5	Found in the majority of mantle cell lymphomas
CD8	Found on cytotoxic T cells. Co-receptor for MHC class I Found on a subset of myeloid dendritic cells
CD14	Cell surface marker for macrophages
CD15	Expressed on Reed-Sternberg cells (along with CD30)
CD16	Bind to the Fc portion of IgG antibodies
CD21	Receptor for Epstein-Barr virus
CD28	Interacts with B7 on antigen presenting cell as costimulation signal
CD45	Protein tyrosine phosphatase present on all leucocytes
CD56	Unique marker for natural killer cells
CD95	Acts as the FAS receptor, involved in apoptosis

Tumour suppressor genes

Basics

- genes which normally control the cell cycle
- loss of function results in an increased risk of cancer
- both alleles must be mutated before cancer occurs

Examples

Gene	Associated cancers
p53	Common to many cancers, Li-Fraumeni syndrome
APC	Colorectal cancer
BRCA1	Breast and ovarian cancer
BRCA2	Breast and ovarian cancer
NF1	Neurofibromatosis
Rb	Retinoblastoma
WT1	Wilm's tumour
Multiple tumor suppressor 1 (MTS-1, p16)	Melanoma

Tumour suppressor genes - loss of function results in an increased risk of cancer

Oncogenes - gain of function results in an increased risk of cancer

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Oncogenes

Oncogenes are cancer promoting genes that are derived from normal genes (proto-oncogenes). Proto-oncogenes play an important physiological role in cellular growth and differentiation. A 'gain of function' results in an increased risk of cancer. Only one mutated copy of the gene is needed for cancer to occur - a dominant effect. They are implicated in the development of up to 20% of human cancers.

Proto-oncogenes may become oncogenes via the following processes:

- Mutation (point mutation)
- Chromosomal translocation
- Increased protein expression

Examples

Gene	Category	Associated cancers
ABL	Cytoplasmic tyrosine kinase	Chronic myeloid leukaemia
c-MYC	Transcription factor	Burkitt's lymphoma
n-MYC	Transcription factor	Neuroblastoma
BCL-2	Apoptosis regulator protein	Follicular lymphoma
RET	Tyrosine kinase receptor	Multiple endocrine neoplasia (types II and III)
RAS	G-protein	Many cancers especially pancreatic
erb-B2 (HER2/neu)	Tyrosine kinase receptor	Breast and ovarian cancer

How are they different from tumour suppressory genes?

Tumour suppressor genes restrict or repress cellular proliferation in normal cells. Their inactivation through mutation or germ line incorporation is implicated in renal, colonic, breast, bladder and many other cancers. One of the best known tumour suppressor genes is p53. p53 gene offers protection by causing apoptosis of damaged cells. Other well known genes include BRCA 1 and 2.

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Tumor suppressor genes - loss of function results in an increased risk of cancer

Oncogenes - gain of function results in an increased risk of cancer

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Complement deficiencies

Complement is a series of proteins that circulate in plasma and are involved in the inflammatory and immune reaction of the body. Complement proteins are involved in chemotaxis, cell lysis and opsonisation

C1 inhibitor (C1-INH) protein deficiency

- causes hereditary angioedema
- C1-INH is a multifunctional serine protease inhibitor
- probable mechanism is uncontrolled release of bradykinin resulting in oedema of tissues

C1q, C1rs, C2, C4 deficiency (classical pathway components)

- predisposes to immune complex disease
- e.g. SLE, Henoch-Schonlein Purpura

C3 deficiency

- causes recurrent bacterial infections

C5 deficiency

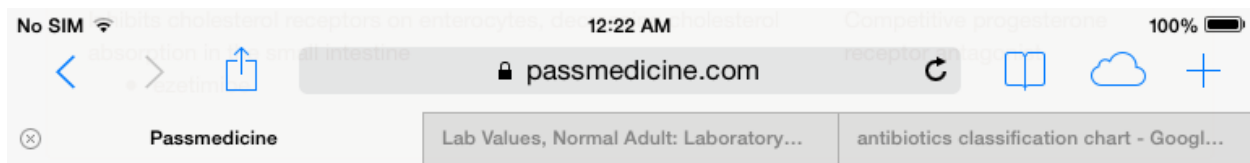
- predisposes to Leiner disease
- recurrent diarrhoea, wasting and seborrhoeic dermatitis

C5-9 deficiency

- encodes the membrane attack complex (MAC)
- particularly prone to *Neisseria meningitidis* infection

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Ezetimibe

Ezetimibe is a lipid-lowering drug which inhibits cholesterol receptors on enterocytes, decreasing cholesterol absorption in the small intestine.

NICE produced guidelines in 2016 on the use of **ezetimibe in primary heterozygous-familial and non-familial hypercholesterolaemia**

- Ezetimibe monotherapy is recommended as an option for treating primary hypercholesterolaemia in adults in whom initial statin therapy is contraindicated or who cannot tolerate statin therapy
- Ezetimibe, coadministered with initial statin therapy, is recommended as an option for treating primary hypercholesterolaemia in adults who have started statin therapy when:
 - → serum total or LDL cholesterol concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy
 - → a change from initial statin therapy to an alternative statin is being considered.

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Whilst p53 can trigger cell cycle arrest to allow DNA to be repaired the encoded proteins do not directly repair DNA.



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p53

p53 is a tumour suppressor gene located on chromosome 17p. It is the most commonly mutated gene in breast, colon and lung cancer

p53 is thought to play a crucial role in the cell cycle, preventing entry into the S phase until DNA has been checked and repaired. It may also be a key regulator of apoptosis

Li-Fraumeni syndrome is a rare autosomal dominant disorder characterised by the early onset of a variety of cancers such as sarcomas and breast cancer. It is caused by mutation in the p53 gene

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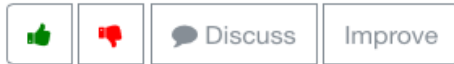
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Prader-Willi syndrome

Prader-Willi syndrome is an example of genetic imprinting where the phenotype depends on whether the deletion occurs on a gene inherited from the mother or father:

- Prader-Willi syndrome if gene deleted from father
- Angelman syndrome if gene deleted from mother

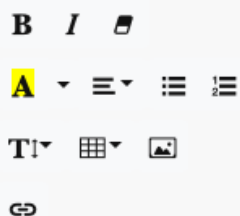
Prader-Willi syndrome is associated with the absence of the active Prader-Willi gene on the long arm of chromosome 15. This may be due to:

- microdeletion of paternal 15q11-13 (70% of cases)
- maternal uniparental disomy of chromosome 15

Features

- hypotonia during infancy
- dysmorphic features
- short stature
- hypogonadism and infertility
- learning difficulties
- childhood obesity
- behavioural problems in adolescence

Next question >



Down's syndrome: epidemiology and genetics

Risk of Down's syndrome with increasing maternal age

Age (years)	Risk
20	1 in 1,500
30	1 in 800
35	1 in 270
40	1 in 100
45	1 in 50 or greater

One way of remembering this is by starting at 1/1,000 at 30 years and then dividing the denominator by 3 (i.e. 3 times more common) for every extra 5 years of age

Cytogenetics

Mode	% of cases	Risk of recurrence
Non-disjunction	94%	1 in 100 if under mother < 35 years
Robertsonian translocation (usually onto 14)	5%	10-15% if mother is translocation carrier 2.5% if father is translocation carrier
Mosaicism	1%	

The chance of a further child with Down's syndrome is approximately 1 in 100 if the mother is less than 35 years old. If the trisomy 21 is a result of a translocation the risk is much higher

Down syndrome: features

Clinical features

- face: upslanting palpebral fissures, epicanthic folds, Brushfield spots in iris, protruding tongue, small ears, round/flat face
- flat occiput
- single palmar crease, pronounced 'sandal gap' between big and first toe
- hypotonia
- congenital heart defects (40-50%, see below)
- duodenal atresia
- Hirschsprung's disease

Cardiac complications

- multiple cardiac problems may be present
- endocardial cushion defect (c. 40%, also known as atrioventricular septal canal defects)
- ventricular septal defect (c. 30%)
- secundum atrial septal defect (c. 10%)
- tetralogy of Fallot (c. 5%)
- isolated patent ductus arteriosus (c. 5%)

Later complications

- subfertility: males are almost always infertile due to impaired spermatogenesis. Females are usually subfertile, and have an increased incidence of problems with pregnancy and labour
- learning difficulties
- short stature
- repeated respiratory infections (+hearing impairment from glue ear)
- acute lymphoblastic leukaemia
- hypothyroidism
- Alzheimer's
- atlantoaxial instability

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Neisseria meningitidis 23%

Salmonella typhi 7%

Patients who have T-cell dysfunction are most at risk from recurrent viral and fungal infections.



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DiGeorge syndrome

DiGeorge syndrome is a primary immunodeficiency disorder caused by T-cell deficiency and dysfunction. It is an example of a microdeletion syndrome

Features

- at risk of viral and fungal infections
- parathyroid gland hypoplasia → hypocalcaemic tetany
- thymus hypoplasia
- T-lymphocyte deficiency/dysfunction

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Large low set ears 19%



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Fragile X syndrome

Fragile X syndrome is a trinucleotide repeat disorder.

Features in males

- learning difficulties
- large low set ears, long thin face, high arched palate
- macroorchidism
- hypotonia
- autism is more common
- mitral valve prolapse

Features in females (who have one fragile chromosome and one normal X chromosome) range from normal to mild

Diagnosis

- can be made antenatally by chorionic villus sampling or amniocentesis
- analysis of the number of CGG repeats using restriction endonuclease digestion and Southern blot analysis

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A subvalvular aortic stenosis is associated with hypertrophic obstructive cardiomyopathy. Aortic sclerosis does not typically cause radiation to the carotids and associated with a more senior demographic. Aortic regurgitation is associated with an early diastolic murmur and valvular aortic stenosis tends to be related to senile calcification or a bicuspid aortic valve.

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Next question >

William's syndrome

William's syndrome is an inherited neurodevelopmental disorder caused by a microdeletion on chromosome 7

Features

- elfin-like facies
- characteristic like affect - very friendly and social
- learning difficulties
- short stature
- transient neonatal hypercalcaemia
- supravalvular aortic stenosis

Diagnosis is made by FISH studies

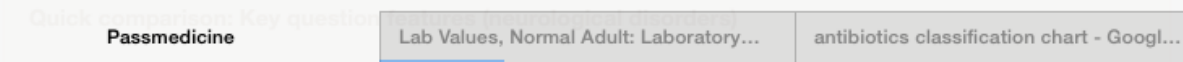
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McCune-Albright syndrome

- cafe-au-lait spots, precocious puberty, short stature

Neurofibromatosis type 1

- cafe-au-lait spots, axillary freckles, iris hamartomas, pheochromocytoma

👍 Relevant to my revision ➤

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McCune-Albright syndrome

McCune-Albright syndrome is an inherited disorder.

Features

- precocious puberty
- cafe-au-lait spots
- polyostotic fibrous dysplasia
- short stature

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Turner's syndrome

Turner's syndrome is a chromosomal disorder affecting around 1 in 2,500 females. It is caused by either the presence of only one sex chromosome (X) or a deletion of the short arm of one of the X chromosomes. Turner's syndrome is denoted as 45,XO or 45,X

Features

- short stature
- shield chest, widely spaced nipples
- webbed neck
- bicuspid aortic valve (15%), coarctation of the aorta (5-10%)
- primary amenorrhoea
- cystic hygroma (often diagnosed prenatally)
- high-arched palate
- short fourth metacarpal
- multiple pigmented naevi
- lymphoedema in neonates (especially feet)

There is also an increased incidence of autoimmune disease (especially autoimmune thyroiditis) and Crohn's disease

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Cutaneous larva migrans - *Ancylostoma Braziliense*

Notes (1/1)

RAS - neurofibromatosis

Notes (0/1)

Childhood syndromes

Below is a list of common features of selected childhood syndromes

Syndrome	Key features
Patau syndrome (trisomy 13)	Microcephalic, small eyes Cleft lip/palate Polydactyly Scalp lesions
Edward's syndrome (trisomy 18)	Micrognathia Low-set ears Rocker bottom feet Overlapping of fingers
Fragile X	Learning difficulties Macrocephaly Long face Large ears Macro-orchidism
Noonan syndrome	Webbed neck Pectus excavatum Short stature Pulmonary stenosis
Pierre-Robin syndrome*	Micrognathia Posterior displacement of the tongue (may result in upper airway obstruction) Cleft palate
Prader-Willi syndrome	Hypotonia Hypogonadism Obesity
William's syndrome	Short stature Learning difficulties Friendly, extrovert personality Transient neonatal hypercalcaemia Supravalvular aortic stenosis

*this condition has many similarities with Treacher-Collins syndrome. One of the key differences is that Treacher-Collins syndrome is autosomal dominant so there is usually a family history of similar problems

HLA associations

HLA antigens are encoded for by genes on chromosome 6. HLA A, B and C are class I antigens whilst DP, DQ, DR are class II antigens. Questions are often based around which diseases have strong HLA associations. The most important associations are listed below:

HLA-A3

- haemochromatosis

HLA-B5

- Behcet's disease

HLA-B27

- ankylosing spondylitis
- Reiter's syndrome
- acute anterior uveitis

HLA-DQ2/DQ8

- coeliac disease

HLA-DR2

- narcolepsy
- Goodpasture's

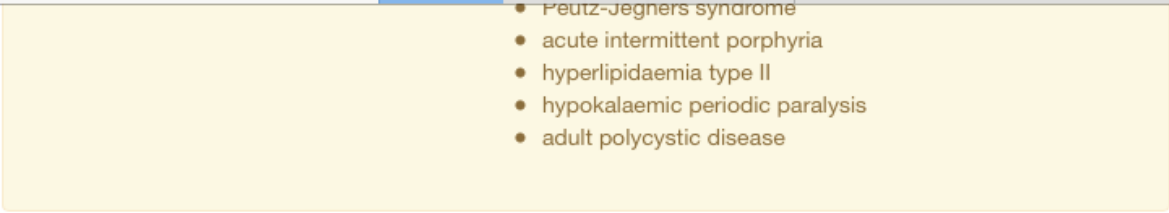
HLA-DR3

- dermatitis herpetiformis
- Sjogren's syndrome
- primary biliary cirrhosis

HLA-DR4

- type 1 diabetes mellitus*
- rheumatoid arthritis

*type 1 diabetes mellitus is associated with HLA-DR3 but is more strongly associated with HLA-DR4.



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Vitamin D-resistant rickets

Vitamin D-resistant rickets is a X-linked dominant condition which usually presents in infancy with failure to thrive. It is caused by impaired phosphate reabsorption in the renal tubules

Features

- failure to thrive
- normal serum calcium, low phosphate, elevated alkaline phosphatase
- x-ray changes: cupped metaphyses with widening of the epiphyses

Diagnosis is made by demonstrating increased urinary phosphate

Management

- high-dose vitamin D supplements
- oral phosphate supplements

Next question >

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X-linked recessive conditions

The following conditions are inherited in a X-linked recessive fashion:

Androgen insensitivity syndrome
Becker muscular dystrophy
Colour blindness
Duchenne muscular dystrophy
Fabry's disease
G6PD deficiency
Haemophilia A,B
Hunter's disease
Lesch-Nyhan syndrome
Nephrogenic diabetes insipidus
Ocular albinism
Retinitis pigmentosa
Wiskott-Aldrich syndrome

The following diseases have varying patterns of inheritance, with the majority being in an X-linked recessive fashion:

Chronic granulomatous disease (in > 70%)

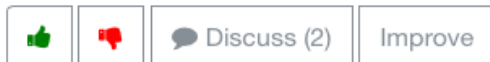
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only have unaffected sons and carrier daughters.

As we now know that mother is not a carrier of the disease there is no chance that any future children could develop haemophilia. You should of course also discuss with him that any daughters that he has will be carriers of the condition.



Next question >

X-linked recessive

In X-linked recessive inheritance only males are affected. An exception to this seen in examinations are patients with Turner's syndrome, who are affected due to only having one X chromosome. X-linked recessive disorders are transmitted by heterozygote females (carriers) and male-to-male transmission is not seen. Affected males can only have unaffected sons and carrier daughters.

Each male child of a heterozygous female carrier has a 50% chance of being affected whilst each female child of a heterozygous female carrier has a 50% chance of being a carrier.

The possibility of an affected father having children with a heterozygous female carrier is generally speaking extremely rare. However, in certain Afro-Caribbean communities G6PD deficiency is relatively common and homozygous females with clinical manifestations of the enzyme defect are seen.

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The risk remains the same for each successive pregnancy 48%

Due to non-penetrance affected individuals do not always have affected parents



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Autosomal dominant

In autosomal dominant diseases:

- both homozygotes and heterozygotes manifest disease (there is no carrier state)
- both males and females affected
- only affected individuals can pass on disease
- disease is passed on to 50% of children
- normally appears in every generation (although see below)
- risk remains same for each successive pregnancy

Complicating factors:

- non-penetrance: lack of clinical signs and symptoms (normal phenotype) despite abnormal gene. E.g. 40% otosclerosis
- spontaneous mutation: new mutation in one of gametes e.g. 80% of individuals with achondroplasia have unaffected parents

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Autosomal dominant conditions

Autosomal recessive conditions are often thought to be 'metabolic' as opposed to autosomal dominant conditions being 'structural', notable exceptions:

- some 'metabolic' conditions such as Hunter's and G6PD are X-linked recessive whilst others such as hyperlipidaemia type II and hypokalaemic periodic paralysis are autosomal dominant
- some 'structural' conditions such as ataxia telangiectasia and Friedreich's ataxia are autosomal recessive

The following conditions are autosomal dominant:

- Achondroplasia
- Acute intermittent porphyria
- Adult polycystic disease
- Antithrombin III deficiency
- Ehlers-Danlos syndrome
- Familial adenomatous polyposis
- Hereditary haemorrhagic telangiectasia
- Hereditary spherocytosis
- Hereditary non-polyposis colorectal carcinoma
- Huntington's disease
- Hyperlipidaemia type II
- Hypokalaemic periodic paralysis
- Malignant hyperthermia
- Marfan's syndromes
- Myotonic dystrophy
- Neurofibromatosis
- Noonan syndrome
- Osteogenesis imperfecta
- Peutz-Jeghers syndrome
- Retinoblastoma
- Romano-Ward syndrome
- Tuberose sclerosis
- Von Hippel-Lindau syndrome
- Von Willebrand's disease*

*type 3 von Willebrand's disease (most severe form) is inherited as an autosomal recessive trait. Around 80% of patients have type 1 disease

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Examples include Huntingdon's disease 8%

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Autosomal recessive

In autosomal recessive inheritance

- only homozygotes are affected
- males and females are equally likely to be affected
- not manifest in every generation - may 'skip a generation'

If two heterozygote parents

- 25% chance of having an affected (homozygote) child
- 50% chance of having a carrier (heterozygote) child
- 25% chance of having an unaffected (i.e. genotypical) child

If one affected parent (i.e. homozygote for gene) and one unaffected (i.e. not a carrier or affected)

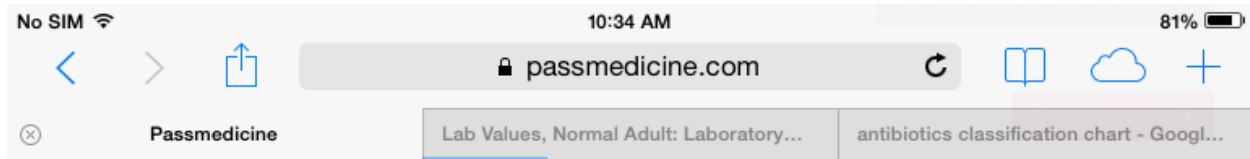
- all the children will be carriers

Autosomal recessive disorders are often metabolic in nature and are generally more life-threatening compared to autosomal dominant conditions

Next question >

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Autosomal recessive conditions

Autosomal recessive conditions are often thought to be 'metabolic' as opposed to autosomal dominant conditions being 'structural', notable exceptions:

- some 'metabolic' conditions such as Hunter's and G6PD are X-linked recessive whilst others such as hyperlipidemia type II and hypokalemic periodic paralysis are autosomal dominant
- some 'structural' conditions such as ataxia telangiectasia and Friedreich's ataxia are autosomal recessive

The following conditions are autosomal recessive:

- Albinism
- Ataxia telangiectasia
- Congenital adrenal hyperplasia
- Cystic fibrosis
- Cystinuria
- Familial Mediterranean Fever
- Fanconi anaemia
- Friedreich's ataxia
- Gilbert's syndrome*
- Glycogen storage disease
- Haemochromatosis
- Homocystinuria
- Lipid storage disease: Tay-Sach's, Gaucher, Niemann-Pick
- Mucopolysaccharidoses: Hurler's
- PKU
- Sickle cell anaemia
- Thalassaemias
- Wilson's disease

*this is still a matter of debate and many textbooks will list Gilbert's as autosomal dominant

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Question

Which one

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Cystic

Type 1

Marfan

Turner's

Cystic fibrosis: features



Presenting features

- neonatal period (around 20%): meconium ileus, less commonly prolonged jaundice
- recurrent chest infections (40%)
- malabsorption (30%): steatorrhoea, failure to thrive
- other features (10%): liver disease

Other features of cystic fibrosis

- short stature
- diabetes mellitus
- delayed puberty
- rectal prolapse (due to bulky stools)
- nasal polyps
- male infertility, female subfertility

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[Cystic fibrosis](#)

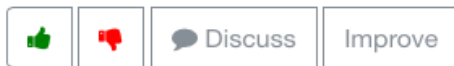
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Cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive disorder causing increased viscosity of secretions (e.g. lungs and pancreas). It is due to a defect in the cystic fibrosis transmembrane conductance regulator gene (CFTR), which codes a cAMP-regulated chloride channel

In the UK 80% of CF cases are due to delta F508 on the long arm of chromosome 7. Cystic fibrosis affects 1 per 2500 births, and the carrier rate is c. 1 in 25

Organisms which may colonise CF patients

- *Staphylococcus aureus*
- *Pseudomonas aeruginosa*
- *Burkholderia cepacia**
- *Aspergillus*

*previously known as *Pseudomonas cepacia*

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High calorie and low fat with pancreatic enzyme supplementation for evening meal	8%
Normal calorie and low fat with pancreatic enzyme supplementation for every meal	18%
High calorie and high fat with pancreatic enzyme supplementation for evening meal	8%
High calorie and high fat with pancreatic enzyme supplementation for every meal	38%

Please see the link for more details.



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Cystic fibrosis: management

Management of cystic fibrosis involves a multidisciplinary approach

Key points

- regular (at least twice daily) chest physiotherapy and postural drainage. Parents are usually taught to do this. Deep breathing exercises are also useful
- high calorie diet, including high fat intake*
- vitamin supplementation
- pancreatic enzyme supplements taken with meals
- heart and lung transplant

*this is now the standard recommendation - previously high calorie, low-fat diets have been recommended to reduce the amount of steatorrhoea

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Trinucleotide repeat disorders

Trinucleotide repeat disorders are genetic conditions caused by an abnormal number of repeats (expansions) of a repetitive sequence of three nucleotides. These expansions are unstable and may enlarge which may lead to an earlier age of onset in successive generations - a phenomenon known as anticipation*. In most cases, an increase in the severity of symptoms is also noted

Examples - note dominance of neurological disorders

- Fragile X (CGG)
- Huntington's (CAG)
- myotonic dystrophy (CTG)
- Friedreich's ataxia* (GAA)
- spinocerebellar ataxia
- spinobulbar muscular atrophy
- dentatorubral pallidoluysian atrophy

*Friedreich's ataxia is unusual in not demonstrating anticipation

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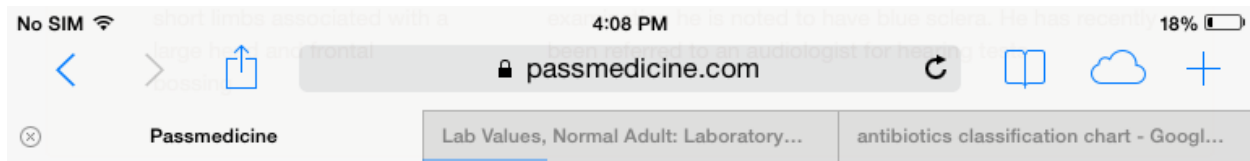
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Huntington disease - causes, symptoms, diagnosis, treatment & pathology

Osmosis - YouTube

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Relevant to my revision >

Less relevant >

Achondroplasia

Achondroplasia is an autosomal dominant disorder associated with short stature. It is caused by a mutation in the fibroblast growth factor receptor 3 (FGFR-3) gene. This results in abnormal cartilage giving rise to:

- short limbs (rhizomelia) with shortened fingers (brachydactyly)
- large head with frontal bossing and narrow foramen magnum
- midface hypoplasia with a flattened nasal bridge
- 'trident' hands
- lumbar lordosis

In most cases (approximately 70%) it occurs as a sporadic mutation. The main risk factor is advancing parental age at the time of conception. Once present it is typically inherited in an autosomal dominant fashion.

Treatment

There is no specific therapy. However, some individuals benefit from limb lengthening procedures. These usually involve application of Ilizarov frames and targeted bone fractures. A clearly defined need and end point is the cornerstone of achieving success with such procedures.

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Congenital heart disease: types

Acyanotic - most common causes

- ventricular septal defects (VSD) - most common, accounts for 30%
- atrial septal defect (ASD)
- patent ductus arteriosus (PDA)
- coarctation of the aorta
- aortic valve stenosis

VSDs are more common than ASDs. However, in adult patients ASDs are the more common new diagnosis as they generally presents later

Cyanotic - most common causes

- tetralogy of Fallot
- transposition of the great arteries (TGA)
- tricuspid atresia

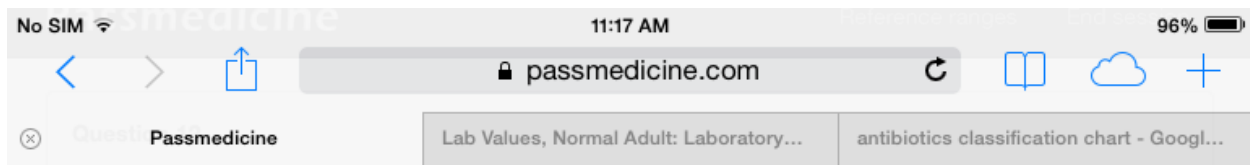
Fallot's is more common than TGA. However, at birth TGA is the more common lesion as patients with Fallot's generally presenting at around 1-2 months

The presence of cyanosis in pulmonary valve stenosis depends very much on the severity and any other coexistent defects.

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What is the mode of inheritance of **acute intermittent porphyria**?

X-linked dominant

Autosomal recessive

Autosomal dominant

X-linked recessive

Quick comparison: Mode of inheritance

Autosomal dominant

- antithrombin III deficiency
- familial adenomatous polyposis
- Marfan's syndromes
- Noonan syndrome
- Ehlers-Danlos syndrome
- achondroplasia
- von Hippel-Lindau syndrome
- Romano-Ward syndrome
- hereditary haemorrhagic telangiectasia
- myotonic dystrophy
- osteogenesis imperfecta
- von Willebrand's disease
- hereditary spherocytosis
- retinoblastoma
- tuberous sclerosis
- Huntington's disease
- hereditary non-polyposis colorectal carcinoma
- neurofibromatosis
- malignant hyperthermia
- Peutz-Jeghers syndrome
- acute intermittent porphyria
- hyperlipidaemia type II
- hypokalaemic periodic paralysis
- adult polycystic disease

Autosomal recessive

- Wilson's disease
- congenital adrenal hyperplasia
- Fanconi anaemia
- alpha-1 antitrypsin deficiency
- albinism
- cystinuria
- mucopolysaccharidoses: Hurler's
- Friedreich's ataxia
- PKU
- glycogen storage disease
- ataxia telangiectasia
- homocystinuria
- cystic fibrosis
- sickle cell anaemia
- familial Mediterranean Fever
- haemochromatosis
- Gilbert's syndrome
- thalassaemias
- lipid storage disease: Tay-Sach's, Gaucher, Niemann-Pick

👍 Relevant to my revision ➔



Question

Hirschsprung's disease



What is the

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Hirschsprung's disease is caused by an aganglionic segment of bowel due to a developmental failure of the parasympathetic Auerbach and Meissner plexuses. Although rare (occurring in 1 in 5,000 births) it is an important differential diagnosis in childhood constipation

Possible presentations

- neonatal period e.g. failure or delay to pass meconium
- older children: constipation, abdominal distension

Associations

- 3 times more common in males
- Down's syndrome

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Hirschsprung disease

Osmosis - YouTube

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Close

Pyloric stenosis

Pyloric stenosis typically presents in the second to fourth weeks of life with vomiting, although rarely may present later at up to four months. It is caused by hypertrophy of the circular muscles of the pylorus

Epidemiology

- incidence of 4 per 1,000 live births
- 4 times more common in males
- 10-15% of infants have a positive family history
- first-borns are more commonly affected

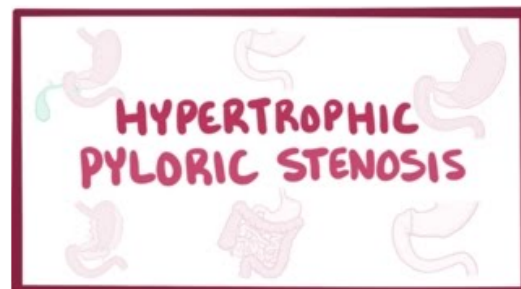
Features

- 'projectile' vomiting, typically 30 minutes after a feed
- constipation and dehydration may also be present
- a palpable mass may be present in the upper abdomen
- hypochlorhaemic, hypokalaemic alkalosis due to persistent vomiting

Diagnosis is most commonly made by ultrasound

Management is with Ramstedt pyloromyotomy

Rich text editor toolbar with buttons for Bold (B), Italic (I), Underline (U), Text color (A), Bulleted list, Numbered list, Indent, Decrease indent, Table, Link, and Image. Below the toolbar is a text input field and a "Save my notes" button.



Next question >

Mitochondrial diseases

Whilst most DNA is found in the cell nucleus, a small amount of double-stranded DNA is present in the mitochondria. It encodes protein components of the respiratory chain and some special types of RNA

Mitochondrial inheritance has the following characteristics:

- inheritance is only via the maternal line as the sperm contributes no cytoplasm to the zygote
- all children of affected males will not inherit the disease
- all children of affected females will inherit it
- generally encode rare neurological diseases
- poor genotype:phenotype correlation - within a tissue or cell there can be different mitochondrial populations - this is known as heteroplasmy)

Histology

- muscle biopsy classically shows 'red, ragged fibres' due to increased number of mitochondria

Examples include:

- Leber's optic atrophy
- MELAS syndrome: mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes
- MERRF syndrome: myoclonus epilepsy with ragged-red fibres
- Kearns-Sayre syndrome: onset in patients < 20 years old, external ophthalmoplegia, retinitis pigmentosa. Ptosis may be seen
- sensorineural hearing loss

Next question >

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Inherited metabolic disorders

Glycogen storage disease

Disorder	Deficient enzyme	Notes
Von Gierke's disease (type I)	Glucose-6-phosphatase	Hepatic glycogen accumulation. Key features include hypoglycaemia, lactic acidosis, hepatomegaly
Pompe's disease (type II)	Lysosomal alpha-1,4-glucosidase	Cardiac, hepatic and muscle glycogen accumulation. Key features include cardiomegaly
Cori disease (type III)	Alpha-1,6-glucosidase (debranching enzyme)	Hepatic, cardiac glycogen accumulation. Key features include muscle hypotonia
McArdle's disease (type V)	Glycogen phosphorylase	Skeletal muscle glycogen accumulation. Key features include myalgia, myoglobulinaemia with exercise

Lysosomal storage disease

Disorder	Defect	Notes
Gaucher's disease	Beta-glucocerebrosidase	Most common lipid storage disorder resulting in accumulation of glucocerebrosidase in the brain, liver and spleen. Key features include hepatosplenomegaly, aseptic necrosis of the femur
Tay-Sachs disease	Hexosaminidase A	Accumulation of GM ₂ ganglioside within lysosomes. Key features include developmental

Lysosomal storage disease

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Tay-Sachs disease	Hexosaminidase A	Accumulation of GM ₂ ganglioside within lysosomes. Key features include developmental delay, cherry red spot on the macula, liver and spleen normal size (<i>cf.</i> Niemann-Pick)
Niemann-Pick disease	Sphingomyelinase	Key features include hepatosplenomegaly, cherry red spot on the macula
Fabry disease	Alpha-galactosidase-A	Accumulation of ceramide trihexoside. Key features include angiokeratomas, peripheral neuropathy of extremities, renal failure
Krabbe's disease	Galactocerebrosidase	Key features include peripheral neuropathy, optic atrophy, globoid cells
Metachromatic leukodystrophy	Arylsulfatase A	Demyelination of the central and peripheral nervous system

Mucopolysaccharidoses

Disorder	Defect	Notes
Hurler syndrome (type I)	Alpha-1-iduronidase	Accumulation of glycosaminoglycans (heparan and dermatan sulfate). Key features include gargoylism, hepatosplenomegaly, corneal clouding

Mucopolysaccharidoses

Disorder	Defect	Notes
Hurler syndrome (type I)	Alpha-1-iduronidase	Accumulation of glycosaminoglycans (heparan and dermatan sulfate). Key features include gargoylism, hepatosplenomegaly, corneal clouding
Hunter syndrome (type II)	Iduronate sulfatase	Accumulation of glycosaminoglycans (heparan and dermatan sulfate). Key features include coarse facial features, behavioural problems/learning difficulties short stature, no corneal clouding

Next question >

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Search

Go

Google search on "Inherited metabolic disorders"

+ Suggest link

Growth hormone

Growth hormone (GH) is an anabolic hormone secreted by the somatotroph cells of the anterior lobe of the pituitary gland. It has actions on multiple organ systems and is important in postnatal growth and development. Growth hormone is also responsible for changes in protein, lipid, and carbohydrate metabolism

	Notes	Further detail
Source	Anterior pituitary	
Function	Postnatal growth and development Numerous actions on protein, carbohydrate and fat metabolism (including increasing lipolysis and gluconeogenesis)	Mechanism of action - acts on a transmembrane receptor for growth factor - binding of GH to the receptor leads to receptor dimerization - acts directly on tissues and also indirectly via insulin-like growth factor 1 (IGF-1), primarily secreted by the liver
Regulation	Increases secretion - growth hormone releasing hormone (GHRH): released in pulses by the hypothalamus - fasting - exercise - sleep Decreases secretion - glucose - somatostatin (itself increased by somatomedins, circulating insulin-like growth factors, IGF-1 and IGF-2)	Conditions associated with GH disorders - excess GH: acromegaly - GH deficiency: resulting in short stature

The answer is Fabry disease. This condition typically presents with proteinuria and is associated with early onset strokes or myocardial infarctions with a typical rash known as angiokeratomas.

CADASIL or cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy is an inherited condition which presents with a history of migraines and multiple strokes. It is not associated with angiokeratomas or corneal whorls. MELAS or mitochondrial encephalopathy with lactic acidosis and stroke symptoms is weakened by the absence of lactic acidosis in the stem. There is no evidence of connective tissue disease in the stem to suggest primary CNS angiitis and cholesterol embolism is typically associated with eosinophilia, livedo reticularis and a precipitant such as preceding angiography.



Next question >

Anderson-Fabry disease

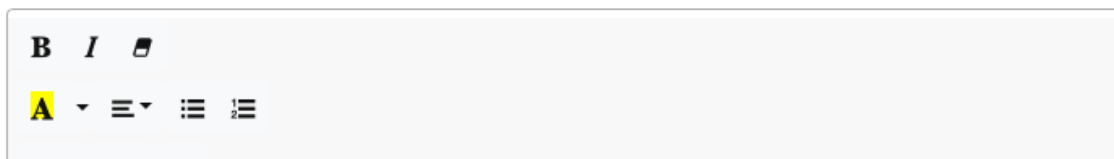
Overview

- X-linked recessive
- deficiency of alpha-galactosidase A

Features

- burning pain/paraesthesia in childhood
- angiokeratomas
- lens opacities
- proteinuria
- early cardiovascular disease

Next question >



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Questions Lab Values, Normal Adult: Laboratory... antibiotics classification chart - Googl...

Next question >

Mitochondrial diseases

Whilst most DNA is found in the cell nucleus, a small amount of double-stranded DNA is present in the mitochondria. It encodes protein components of the respiratory chain and some special types of RNA

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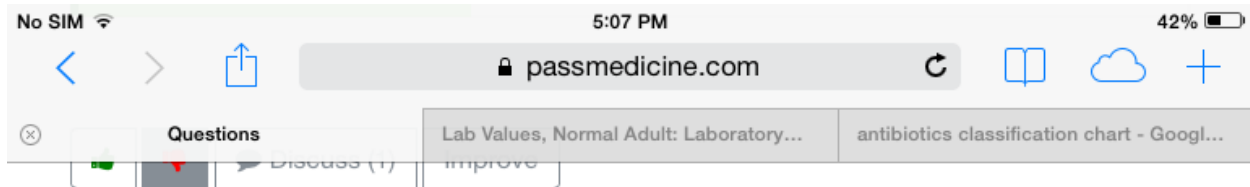
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- sensorineural hearing loss

Next question >

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Galactosaemia

Galactosaemia is a rare autosomal recessive condition caused by the absence of galactose-1-phosphate uridyl transferase. This results in intracellular accumulation of galactose-1-phosphate

Features

- jaundice
- failure to thrive
- hepatomegaly
- cataracts
- hypoglycaemia after exposure to galactose
- Fanconi syndrome

Diagnosis

- urine reducing substances

Management is with a galactose free diet

Next question >

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Alpha-thalassaemia

Alpha-thalassaemia is due to a deficiency of alpha chains in haemoglobin

Overview

- 2 separate alpha-globulin genes are located on each chromosome 16

Clinical severity depends on the number of alpha chains present

If 1 or 2 alpha chains are absent then the blood picture would be hypochromic and microcytic, but the Hb level would be typically normal

Loss of 3 alpha chains results in a hypochromic microcytic anaemia with splenomegaly. This is known as Hb H disease

If all 4 alpha chains absent (i.e. homozygote) then death in utero (hydrops fetalis, Bart's hydrops)

Next question >

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Anaesthetic agents

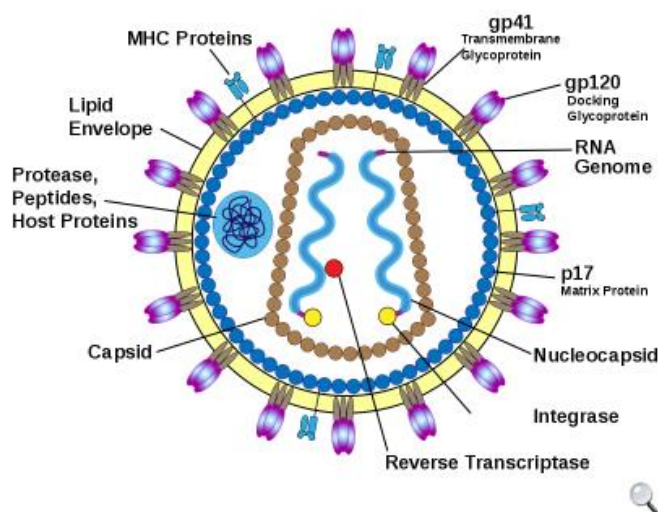
The table below summarises some of the more commonly used IV induction agents

Agent	Specific features
Propofol	• Rapid onset of anaesthesia • Pain on IV injection • Rapidly metabolised with little accumulation of metabolites • Proven anti emetic properties • Moderate myocardial depression • Widely used especially for maintaining sedation on ITU, total IV anaesthesia and for daycase surgery
Sodium thiopentone	• Extremely rapid onset of action making it the agent of choice for rapid sequence of induction • Marked myocardial depression may occur • Metabolites build up quickly • Unsuitable for maintenance infusion • Little analgesic effects
Ketamine	• May be used for induction of anaesthesia • Has moderate to strong analgesic properties • Produces little myocardial depression making it a suitable agent for anaesthesia in those who are haemodynamically unstable • May induce state of dissociative anaesthesia resulting in nightmares
Etomidate	• Has favorable cardiac safety profile with very little haemodynamic instability • No analgesic properties • Unsuitable for maintaining sedation as prolonged (and even brief) use may result in adrenal suppression • Post operative vomiting is common

HIV: the virus

Basics

- HIV is a RNA retrovirus of the lentivirus genus (lentiviruses are characterized by a long incubation period)
- two variants - HIV-1 and HIV-2
- HIV-2 is more common in west Africa, has a lower transmission rate and is thought to be less pathogenic with a slower progression to AIDS



Basics structure

- spherical in shape with two copies of single-stranded RNA enclosed by a capsid of the viral protein p24
- a matrix composed of viral protein p17 surrounds the capsid
- envelope proteins: gp120 and gp41
- pol gene encodes for viral enzymes reverse transcriptase, integrase and HIV protease

Cell entry

- HIV can infect CD4 T cells, macrophages and dendritic cells
- gp120 binds to CD4 and CXCR4 on T cells and CD4 and CCR5 on macrophages
- mutations in CCR5 can give immunity to HIV

Replication

Basics structure

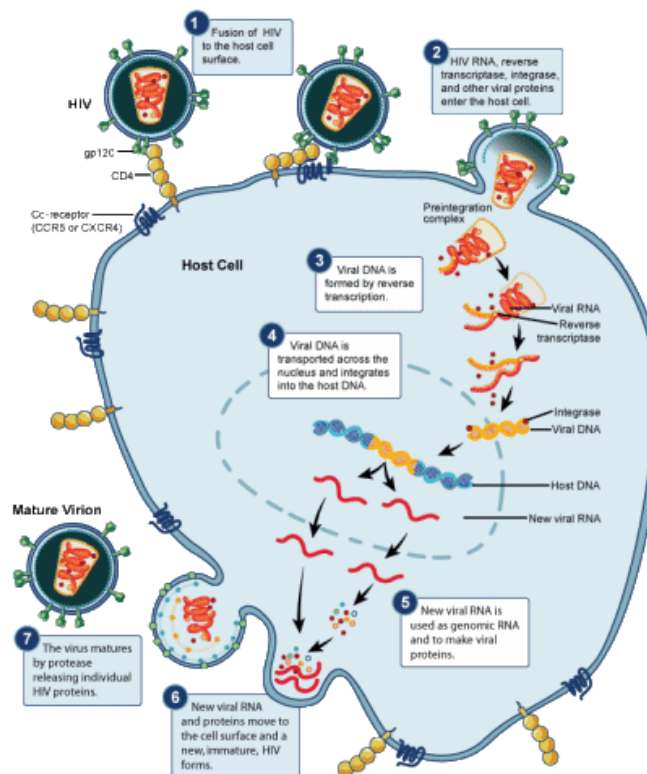
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Replication

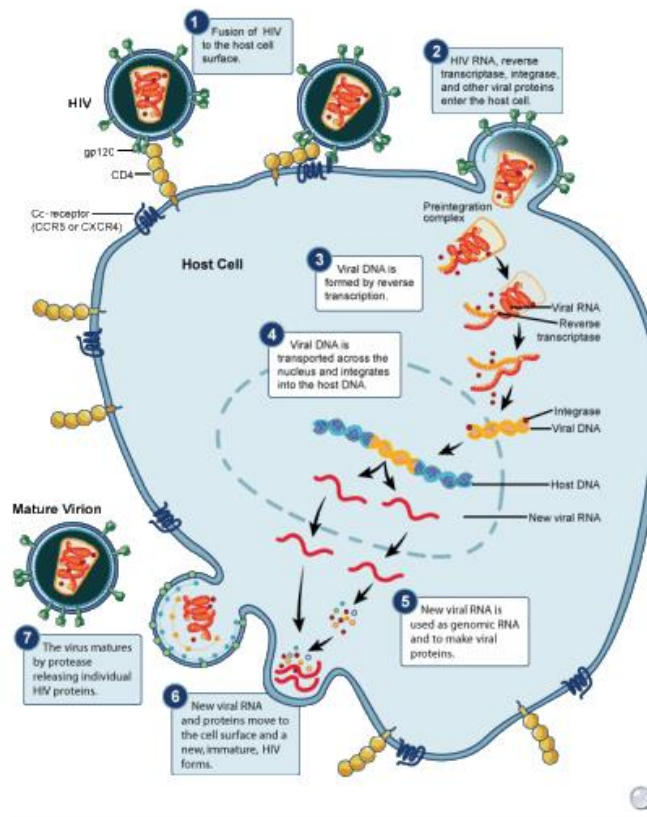
- after entering a cell the enzyme reverse transcriptase creates dsDNA from the RNA for integration into the host cell's genome



HIV: immunology

The following immunological changes are seen in progressive HIV:

- reduction in CD4 count
- increase B2-microglobulin
- decreased IL-2 production
- polyclonal B-cell activation
- decrease NK cell function
- reduced delayed hypersensitivity responses



An illustration model of the HIV Replication Cycle. Each step of the cycle is numbered and concisely described. Credit: NIAID

Next question >

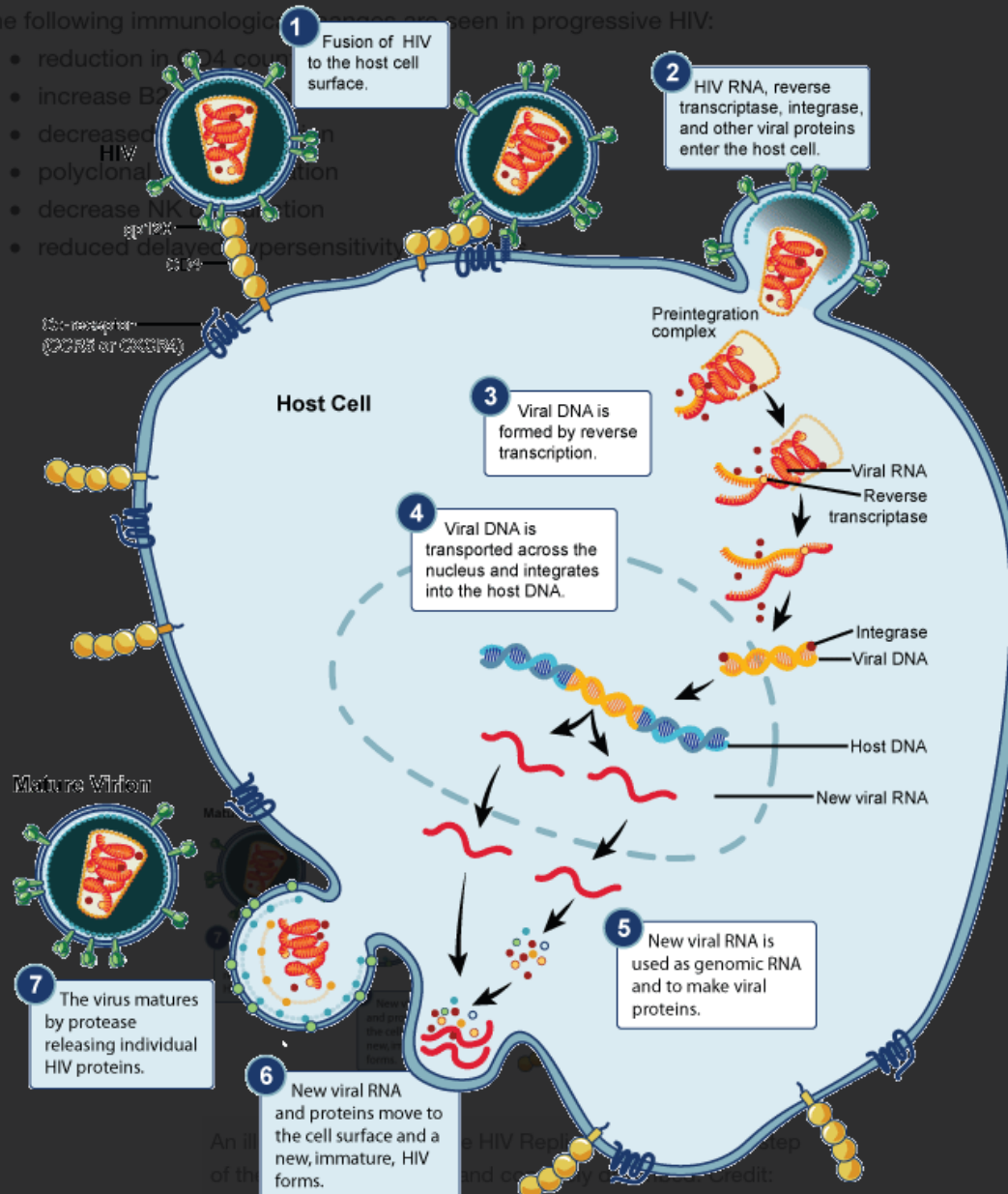


HIV: immunology

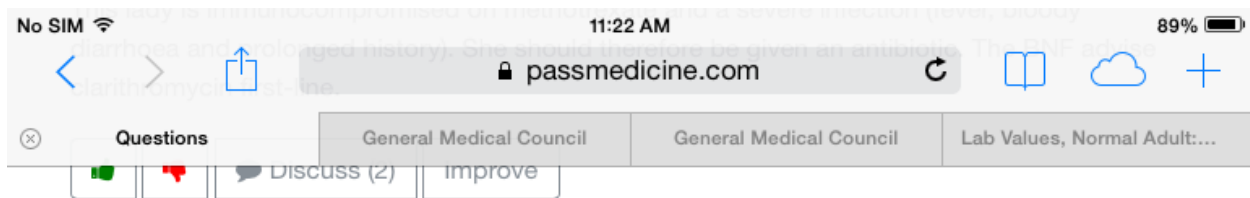


The following immunologic changes are seen in progressive HIV:

- reduction in CD4 count
- increase B220+ cells
- decreased CD8+ T cells
- polyclonal B cell activation
- decrease NK cell cytotoxicity
- reduced delayed hypersensitivity



Next question >



Next question >

Campylobacter

Campylobacter is the commonest bacterial cause of infectious intestinal disease in the UK. The majority of cases are caused by the Gram-negative bacillus *Campylobacter jejuni*. It is spread by the faecal-oral route and has an incubation period of 1-6 days.

Features

- prodrome: headache malaise
- diarrhoea: often bloody
- abdominal pain

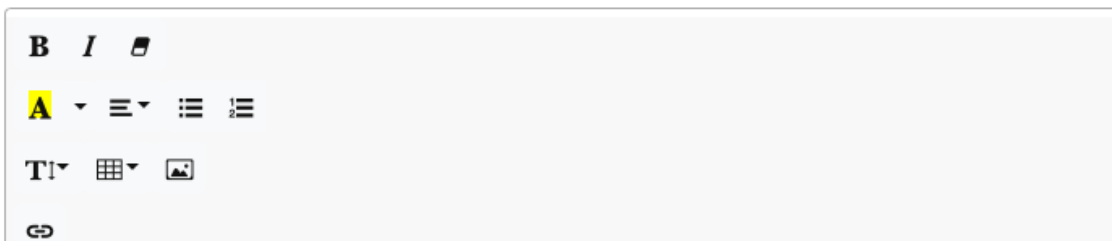
Management

- usually self-limiting
- the BNF advises treatment if severe or the patient is immunocompromised. Clinical Knowledge summaries also recommend antibiotics if severe symptoms (high fever, bloody diarrhoea, or more than eight stools per day) or symptoms have last more than one week
- the first-line antibiotic is clarithromycin

Complications

- Guillain-Barre syndrome may follow *Campylobacter jejuni* infections
- Reiter's syndrome
- septicaemia, endocarditis, arthritis

Next question >



Temporal artery biopsy

- Superficial temporal artery is a terminal branch of the external carotid artery

Main indication

- Temporal arteritis

American College of Rheumatology guidelines recommend a temporal artery biopsy if:

- Age of onset older than 50 years
- New-onset headache or localized head pain
- Temporal artery tenderness to palpation or reduced pulsation
- ESR > 50 mm/h

Histopathology

- Vessel wall granulomatous arteritis with mononuclear cell infiltrates and giant cell formation

Procedure

- Position: supine, head 45 degrees
- USS doppler to locate the superficial temporal artery or palpate
- Local anaesthetic
- Artery within temporoparietal fascia
- Clamp and ligate the vessel
- Cut 3-5cm
- Ligate the remaining ends with absorbable suture
- Close the skin

Contraindication

Glucocorticoid therapy > 30 days

Risks

Injury to facial or auriculotemporal nerve

Next question >

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Reference ranges

End session

Question

A 3-year-old child presents with a fever, malaise, and a rash. The rash is described as 'slapped-cheek' and is spreading to the proximal arms and extensor surfaces. What is the most likely diagnosis?

287 facts

Score for this question

3 in a row

Key facts

A child with a fever and a rash

Hypothalamic

APL

Childhood infections

The table below summarises the main characteristics of childhood infections

Infection	Features
Chickenpox	Fever initially Itchy, rash starting on head/trunk before spreading. Initially macular then papular then vesicular Systemic upset is usually mild
Measles	Prodrome: irritable, conjunctivitis, fever Koplik spots: white spots ('grain of salt') on buccal mucosa Rash: starts behind ears then to whole body, discrete maculopapular rash becoming blotchy & confluent
Mumps	Fever, malaise, muscular pain Parotitis ('earache', 'pain on eating'): unilateral initially then becomes bilateral in 70%
Rubella	Rash: pink maculopapular, initially on face before spreading to whole body, usually fades by the 3-5 day Lymphadenopathy: suboccipital and postauricular
Erythema infectiosum	Also known as fifth disease or 'slapped-cheek syndrome' Caused by parvovirus B19 Lethargy, fever, headache 'Slapped-cheek' rash spreading to proximal arms and extensor surfaces
Scarlet fever	Reaction to erythrogenic toxins produced by Group A haemolytic streptococci Fever, malaise, tonsillitis 'Strawberry' tongue Rash - fine punctate erythema sparing face
Hand, foot and mouth disease	Caused by the coxsackie A16 virus Mild systemic upset: sore throat, fever Vesicles in the mouth and on the palms and soles of the feet



Pass

Scarlet fever



Session

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Down

Scarlet fever is a reaction to erythrogenic toxins produced by Group A haemolytic streptococci (usually *Streptococcus pyogenes*). It is more common in children aged 2 - 6 years with the peak incidence being at 4 years.

Scarlet fever is spread via the respiratory route by inhaling or ingesting respiratory droplets or by direct contact with nose and throat discharges, (especially during sneezing and coughing).

Scarlet fever has an incubation period of 2-4 days and typically presents with:

- fever: typically lasts 24 to 48 hours
- malaise
- tonsillitis
- 'strawberry' tongue
- rash - fine punctate erythema ('pinhead') which generally appears first on the torso and spares the face although children often have a flushed appearance with perioral pallor. The rash often has a rough 'sandpaper' texture. Desquamation occurs later in the course of the illness, particularly around the fingers and toes



© Image used on license from DermNet NZ



Diagnosis

- a throat swab is normally taken but antibiotic treatment should be commenced immediately, rather than waiting for the results

Management

- oral penicillin V for 10 days
- patients who have a penicillin allergy should be given azithromycin
- children can return to school 24 hours after commencing antibiotics
- scarlet fever is a notifiable disease



immediately, rather than waiting for the results

Management

- oral penicillin V for 10 days
- patients who have a penicillin allergy should be given azithromycin
- children can return to school 24 hours after commencing antibiotics
- scarlet fever is a notifiable disease

Scarlet fever is usually a mild illness but may be complicated by:

- otitis media: the most common complication
- rheumatic fever: typically occurs 20 days after infection
- acute glomerulonephritis: typically occurs 10 days after infection



Image sourced from Wikipedia

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Question 13

Which one

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Kawasaki disease



Kawasaki disease is a type of vasculitis which is predominately seen in children. Whilst Kawasaki disease is uncommon it is important to recognise as it may cause potentially serious complications, including coronary artery aneurysms

Features

- high-grade fever which lasts for > 5 days. Fever is characteristically resistant to antipyretics
- conjunctival injection
- bright red, cracked lips
- strawberry tongue
- cervical lymphadenopathy
- red palms of the hands and the soles of the feet which later peel

Kawasaki disease is a clinical diagnosis as there is no specific diagnostic test

Management

- high-dose aspirin*
- intravenous immunoglobulin
- echocardiogram (rather than angiography) is used as the initial screening test for coronary artery aneurysms

Complications

- coronary artery aneurysm

*Kawasaki disease is one of the few indications for the use of aspirin in children. Due to the risk of Reye's syndrome aspirin is normally contraindicated in children.

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[Enterobius vermicularis infection](#)

Quick comparison: Key question features (infections)

Mucormycosis

- black necrotic eshar on face, diabetic

Ancyclostoma Braziliense

- cutaneous larva migrans

Relevant to my revision >

Less relevant >

Mucormycosis

Mucormycosis is a fungal infection that is more commonly seen in poorly controlled diabetes. It typically infects the sinuses, lungs and brain.

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Reference ranges End session

Diarrhoea in children

Gastroenteritis

- main risk is severe dehydration
- most common cause is rotavirus - typically accompanied by fever and vomiting for the first 2 days. The diarrhoea may last up to a week
- treatment is rehydration

Chronic diarrhoea

Infants

- most common cause in the developed world is cows' milk intolerance
- toddler diarrhoea: stools vary in consistency, often contain undigested food
- coeliac disease
- post-gastroenteritis lactose intolerance

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Acute Gastroenteritis (Paediatrics) Overview

Armando Hasudungan - YouTube

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Cutaneous larva migrans

Cutaneous Larva Migrans is caused by the infection of the dog hook worm *Ancylostoma Braziliense*.

Man is an accidental dead end host and so the larva is unable to migrate to the lungs and intestine. The intensely itchy trial is a result of the subcutaneous migration of the frustrated larva.

Management is with Albendazole or Ivermectin.

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Center for Disease Control

↑ 0 ↓ 0

[Cutaneous Larva Migrans](#)

Close

Cutaneous larva migrans - *Ancylostoma Braziliense*

[Notes](#) (1/1)

RAS - neurofibromatosis

[Notes](#) (0/1)

Multiple tumor suppressor 1 (MTS-1, p16) - melanoma

[Notes](#) (1/1)

Measles

Measles is now rarely seen in the developed world following the adoption of immunisation programmes. Outbreaks are occasionally seen, particularly when vaccinations rates drop, for example after the MMR controversy of the early 2000's.

Overview

- RNA paramyxovirus
- spread by droplets
- infective from prodrome until 4 days after rash starts
- incubation period = 10-14 days

Features

- prodrome: irritable, conjunctivitis, fever
- Koplik spots (before rash): white spots ('grain of salt') on buccal mucosa
- rash: starts behind ears then to whole body, discrete maculopapular rash becoming blotchy & confluent



© Image used on license from DermNet NZ

Koplik spots

Investigations

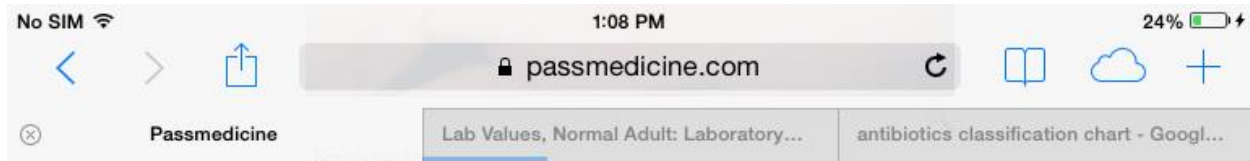
- IgM antibodies can be detected within a few days of rash onset

Management

- mainly supportive
- admission may be considered in immunosuppressed or pregnant patients
- notifiable disease → inform public health

Complications

- encephalitis typically occurs 1-2 weeks following the onset of the illness



Investigations

- IgM antibodies can be detected within a few days of rash onset

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- mainly supportive
- admission may be considered in immunosuppressed or pregnant patients
- notifiable disease → inform public health

Complications

- encephalitis: typically occurs 1-2 weeks following the onset of the illness)
- subacute sclerosing panencephalitis: very rare, may present 5-10 years following the illness
- febrile convulsions
- giant cell pneumonia
- keratoconjunctivitis, corneal ulceration
- diarrhoea
- increased incidence of appendicitis
- myocarditis



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The rash typically starts behind the ears and then spreads to the whole body

Management of contacts

- if a child not immunized against measles comes into contact with measles then MMR should be offered (vaccine-induced measles antibody develops more rapidly than that following natural infection)
- this should be given within 72 hours

Helminths

Nematodes (roundworms)

Worm	Notes	Treatment
<i>Strongyloides stercoralis</i>	Larvae are present in soil and gain access to the body by penetrating the skin Features include diarrhoea, abdominal pain, papulovesicular lesions where the skin has been penetrated by infective larvae e.g. soles of feet and buttocks, larva currens: pruritic, linear, urticarial rash, if the larvae migrate to the lungs a pneumonitis similar to Loeffler's syndrome may be triggered	Ivermectin and -bendazoles are used
<i>Enterobius vermicularis</i> (pinworm)	Threadworm infestation is asymptomatic in around 90% of cases, possible features include perianal itching, particularly at night; girls may have vulval symptoms Diagnosis may be made by the applying sticky plastic tape to the perianal area and sending it to the laboratory for microscopy to see the eggs	-bendazoles
<i>Ancylostoma duodenale</i> , <i>Necator americanus</i> (hookworms)	Larvae penetrate skin of feet; gastrointestinal infection → anaemia Thin-shelled ova	-bendazoles
<i>Loa loa</i>	Transmission by deer fly and mango fly Causes red itchy swellings below the skin called 'Calabar swellings', may be observed when crossing conjunctivae	Diethylcarbamazine
<i>Trichinella spiralis</i>	Typically develops after eating raw pork Features include fever, periorbital oedema and myositis (larvae encyst in muscle)	-bendazoles
<i>Onchocerca volvulus</i>	Causes 'river blindness'. Spread by female blackflies Features include blindness, hyperpigmented skin and possible allergic reaction to microfilaria	Ivermectin rIVERblindness = IVERmectin
<i>Wuchereria</i>	Transmission by female mosquito	Diethylcarbamazine

Worm	Notes	Treatment
<i>Echinococcus granulosus</i>	Transmission through ingestion of eggs in dog faeces. Definite host is dog, which ingests hydatid cysts from sheep, who act as an intermediate host.	-bendazoles

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Lab Values, Normal Adult: Laboratory...

antibiotics classification chart - Googl...

Cestodes (tapeworms)

Worm	Notes	Treatment
Echinococcus granulosus	Transmission through ingestion of eggs in dog faeces. Definite host is dog, which ingests hydatid cysts from sheep, who act as an intermediate host. Often seen in farmers. Features include liver cysts and anaphylaxis if cyst ruptures (e.g. during surgical removal)	-bendazoles
Taenia solium	Often transmitted after eating undercooked pork. Causes cysticercosis and neurocysticercosis, mass lesions in the brain 'swiss cheese appearance'	-bendazoles
Fasciola hepatica (the liver fluke)	May cause biliary obstruction	Triclabendazole

Trematodes (flukes)

Worm	Notes	Treatment
Schistosoma haematobium	Hosted by snails, which release cercariae that penetrate skin. Causes 'swimmer's itch' - frequency, haematuria. Risk factor for squamous cell bladder cancer	Praziquantel
Paragonimus westermani	Caused by undercooked crabmeat, results in secondary bacterial infection of lungs	Praziquantel
Clonorchis sinensis	Caused by undercooked fish Features include biliary tract inflammation. Known risk factor for cholangiocarcinoma	Praziquantel

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Coarctation of the aorta is a congenital narrowing of the aorta, usually occurring just distal to the subclavian artery origin. It is characterized by a localized constriction of the aortic lumen, which can lead to hypertension in the upper extremities and hypotension in the lower extremities. The condition is often associated with a bicuspid aortic valve and may require surgical intervention to relieve the obstruction and prevent complications such as aortic aneurysm or dissection.

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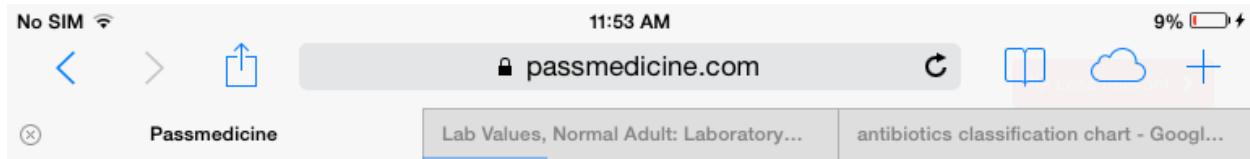
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Breast feeding: contraindications

The major breastfeeding contraindications tested in exams relate to drugs (see below). Other contraindications of note include:

- galactosaemia
- viral infections - this is controversial with respect to HIV in the developing world. This is because there is such an increased infant mortality and morbidity associated with bottle feeding that some doctors think the benefits outweigh the risk of HIV transmission

Drug contraindications

The following drugs can be given to mothers who are breastfeeding:

- antibiotics: penicillins, cephalosporins, trimethoprim
- endocrine: glucocorticoids (avoid high doses), levothyroxine*
- epilepsy: sodium valproate, carbamazepine
- asthma: salbutamol, theophyllines
- psychiatric drugs: tricyclic antidepressants, antipsychotics**
- hypertension: beta-blockers, hydralazine
- anticoagulants: warfarin, heparin
- digoxin

The following drugs should be avoided:

- antibiotics: ciprofloxacin, tetracycline, chloramphenicol, sulphonamides
- psychiatric drugs: lithium, benzodiazepines
- aspirin
- carbimazole
- methotrexate
- sulphonylureas
- cytotoxic drugs
- amiodarone

*the BNF advises that the amount is too small to affect neonatal hypothyroidism screening

**clozapine should be avoided

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Congenital infections

The major congenital infections encountered in examinations are rubella, toxoplasmosis and cytomegalovirus

Cytomegalovirus is the most common congenital infection in the UK. Maternal infection is usually asymptomatic

	Rubella	Toxoplasmosis	Cytomegalovirus
Characteristic features	Sensorineural deafness Congenital cataracts Congenital heart disease (e.g. patent ductus arteriosus) Glaucoma	Cerebral calcification Chorioretinitis Hydrocephalus	Growth retardation Purpuric skin lesions
Other features	Growth retardation Hepatosplenomegaly Purpuric skin lesions 'Salt and pepper' chorioretinitis Microphthalmia Cerebral palsy	Anaemia Hepatosplenomegaly Cerebral palsy	Sensorineural deafness Encephalitis/seizures Pneumonitis Hepatosplenomegaly Anaemia Jaundice Cerebral palsy

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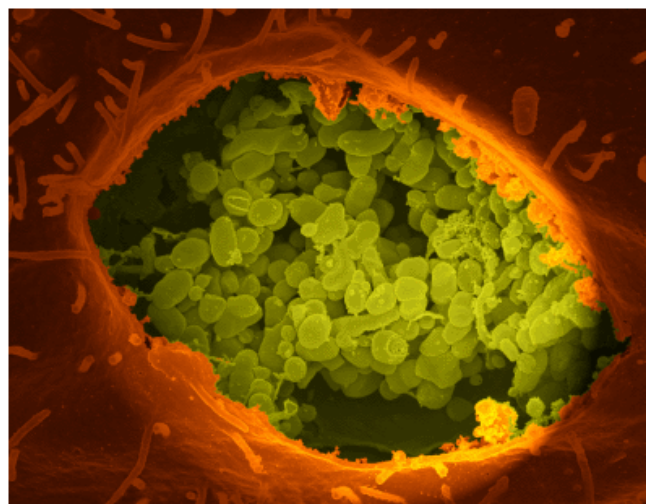
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Rickettsiae

Rickettsiae are Gram-negative obligate intracellular parasites. Types of rickettsiae cause a variety of diseases that are typically characterised by fever, headache and rash. A notable exception is Q fever (cause by *Coxiella burnetti* which causes pneumonia but no rash. The Weil-Felix reaction is positive except in Q fever. Rickettsial diseases are all treated with tetracyclines.

Disease	Cause	Vector	Notes
Rocky Mountain spotted fever	<i>Rickettsia rickettsii</i>	Tick	Headache and fever are common Rash starts on the peripheries (wrist, ankles) before spreading centrally. It is initially maculopapular before becoming vasculitic Endemic to east coast of US
Q fever	<i>Coxiella burnetti</i>	No vector	No rash but causes pneumonia
Endemic typhus	<i>Rickettsia typhi</i>	Flea	Rash starts centrally then spreads to the peripheries
Epidemic typhus	<i>Rickettsia prowazekii</i>	Human body louse	
Ehrlichiosis	<i>Ehrlichia</i>	Tick	



Bronchiolitis

Bronchiolitis is a condition characterised by acute bronchiolar inflammation. Respiratory syncytial virus (RSV) is the pathogen in 75-80% of cases. NICE released guidelines on bronchiolitis in 2015. Please see the link for more details.

Epidemiology

- most common cause of a serious lower respiratory tract infection in < 1yr olds (90% are 1-9 months, with a peak incidence of 3-6 months). Maternal IgG provides protection to newborns against RSV
- higher incidence in winter

Basics

- respiratory syncytial virus (RSV) is the pathogen in 75-80% of cases
- other causes: mycoplasma, adenoviruses
- may be secondary bacterial infection
- more serious if bronchopulmonary dysplasia (e.g. Premature), congenital heart disease or cystic fibrosis

Features

- coryzal symptoms (including mild fever) precede:
- dry cough
- increasing breathlessness
- wheezing, fine inspiratory crackles (not always present)
- feeding difficulties associated with increasing dyspnoea are often the reason for hospital admission

NICE recommend immediate referral (usually by 999 ambulance) if they have any of the following:

- apnoea (observed or reported)
- child looks seriously unwell to a healthcare professional
- severe respiratory distress, for example grunting, marked chest recession, or a respiratory rate of over 70 breaths/minute
- central cyanosis
- persistent oxygen saturation of less than 92% when breathing air.

NICE recommend that clinicians 'consider' referring to hospital if any of the following apply:

- a respiratory rate of over 60 breaths/minute
- difficulty with breastfeeding or inadequate oral fluid intake (50-75% of usual volume 'taking account of risk factors and using clinical judgement')
- clinical dehydration.

Investigation

- immunofluorescence of nasopharyngeal secretions may show RSV

Management is largely supportive

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bacterial infection passmedicine.com

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Features

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- clinical dehydration.

Investigation

- immunofluorescence of nasopharyngeal secretions may show RSV

Management is largely supportive

- humidified oxygen is given via a head box and is typically recommended if the oxygen saturations are persistently < 92%
- nasogastric feeding may be need if children cannot take enough fluid/feed by mouth
- suction is sometimes used for excessive upper airway secretions

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Croup

Croup is a form of upper respiratory tract infection seen in infants and toddlers. It is characterised by stridor which is caused by a combination of laryngeal oedema and secretions. Parainfluenza viruses account for the majority of cases.

Epidemiology

- peak incidence at 6 months - 3 years
- more common in autumn

Features

- stridor
- barking cough (worse at night)
- fever
- coryzal symptoms

Clinical Knowledge Summaries (CKS) suggest using the following criteria to grade the severity*:

Mild	Moderate	Severe
Occasional barking cough	Frequent barking cough	Frequent barking cough
No audible stridor at rest	Easily audible stridor at rest	Prominent inspiratory (and occasionally, expiratory) stridor at rest
No or mild suprasternal and/or intercostal recession	Suprasternal and sternal wall retraction at rest	Marked sternal wall retractions
The child is happy and is prepared to eat, drink, and play	No or little distress or agitation	Significant distress and agitation, or lethargy or restlessness (a sign of hypoxaemia)
	The child can be placated and is interested in its surroundings	Tachycardia occurs with more severe obstructive symptoms and hypoxaemia

CKS suggest admitting any child with moderate or severe croup. Other features which should prompt admission include:

- < 6 months of age
- known upper airway abnormalities (e.g. Laryngomalacia, Down's syndrome)
- uncertainty about diagnosis (important differentials include acute epiglottitis, bacterial tracheitis, peritonsillar abscess and foreign body inhalation)

Management

- CKS recommend giving a single dose of oral dexamethasone (0.15mg/kg) to all

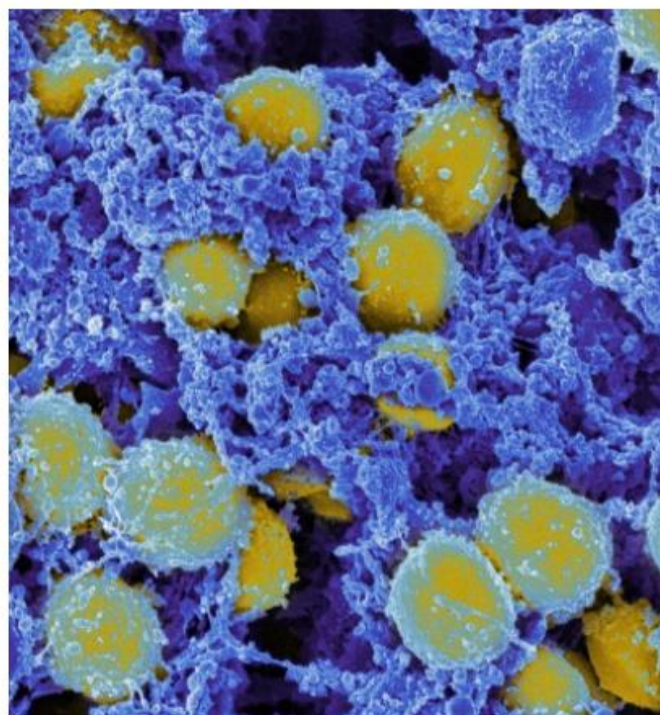
Staphylococci

Staphylococci are a common type of bacteria which are often found normal commensal organisms but may also cause invasive disease. Some basic facts include:

- Gram-positive cocci
- facultative anaerobes
- produce catalase

The two main types of Staphylococci you need to know about are *Staphylococcus aureus* and *Staphylococcus epidermidis*.

<i>Staphylococcus aureus</i>	<i>Staphylococcus epidermidis</i>
• Coagulase-positive • Causes skin infections (e.g. cellulitis), abscesses, osteomyelitis, toxic shock syndrome	• Coagulase-negative • Cause of central line infections and infective endocarditis



Scanning electromicrograph of *Staphylococcus aureus* bacteria. Credit: NIAID



Herpes simplex virus

There are two strains of the herpes simplex virus (HSV) in humans: HSV-1 and HSV-2. Whilst it was previously thought HSV-1 accounted for oral lesions (cold sores) and HSV-2 for genital herpes it is now known there is considerable overlap

Features

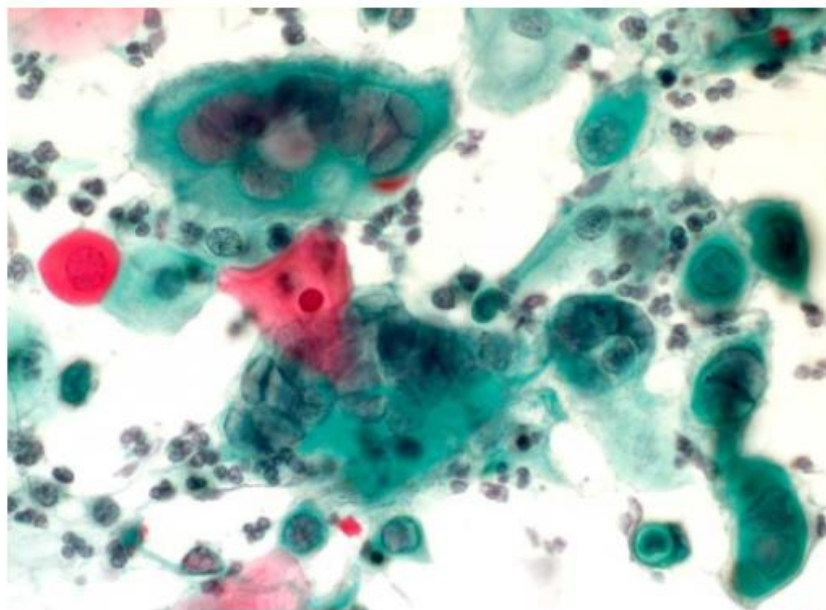
- primary infection: may present with a severe gingivostomatitis
- cold sores
- painful genital ulceration

Management

- gingivostomatitis: oral aciclovir, chlorhexidine mouthwash
- cold sores: topical aciclovir although the evidence base for this is modest
- genital herpes: oral aciclovir. Some patients with frequent exacerbations may benefit from longer term aciclovir

Pregnancy

- elective caesarean section at term is advised if a primary attack of herpes occurs during pregnancy at greater than 28 weeks gestation
- women with recurrent herpes who are pregnant should be treated with suppressive therapy and be advised that the risk of transmission to their baby is low



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Hand, foot and mouth disease



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Hand, foot and mouth disease is a self-limiting condition affecting children. It is caused by the intestinal viruses of the Picornaviridae family (most commonly coxsackie A16 and enterovirus 71). It is very contagious and typically occurs in outbreaks at nursery

Clinical features

- mild systemic upset: sore throat, fever
- oral ulcers
- followed later by vesicles on the palms and soles of the feet



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Management

- general advice about hydration and analgesia
- reassurance no link to disease in cattle
- children do not need to be excluded from school*

*The HPA recommends that children who are unwell should be kept off school until they feel better. They also advise that you contact them if you suspect that there may be a large outbreak.

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Exotoxins and endotoxins

Exotoxins are secreted by bacteria where as endotoxins are only released following lysis of the cell. Exotoxins are generally released by Gram positive bacteria with the notable exceptions of *Vibrio cholerae* and some strains of *E. coli*

It is possible to classify exotoxins by their primary effects:

- pyrogenic toxins
- enterotoxins
- neurotoxins
- tissue invasive toxins
- miscellaneous toxins

Pyrogenic toxins

Pyrogenic toxins stimulate the release of endogenous cytokines resulting in fever, rash etc. They are superantigens which bridge the MHC class II protein on antigen-presenting cells with the T cell receptor on the surface of T cells resulting in massive cytokine release.

Organism	Toxin	Notes
<i>Staphylococcus aureus</i>	Toxic shock syndrome (TSST-1 superantigen) toxin	Results in high fever, hypotension, exfoliative rash
<i>Streptococcus pyogenes</i>	Streptococcal pyrogenic exotoxin A & C	Results in scarlet fever

Enterotoxins

Enterotoxins act on the gastrointestinal tract causing one of two patterns of illness:

- diarrhoeal illness
- vomiting illness ('food poisoning')

Enterotoxins

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- diarrhoeal illness
- vomiting illness ('food poisoning')

Organism	Toxin	Notes
<i>Vibrio cholerae</i>	Cholera toxin	Causes activation of adenylate cyclase (via G_s) leading to increases in cAMP levels, which in turn leads to increased chloride secretion and reduced sodium absorption
<i>Shigella dysenteriae</i>	Shiga toxin	Inactivates 60S ribosome → epithelial cell death
<i>Escherichia coli</i>	1. Heat labile toxin	1. Activates adenylate cyclase (via G_s), increasing cAMP → watery diarrhoea
	2. Heat stable toxin	2. Activates guanylate cyclase, increasing cGMP → watery diarrhoea
<i>Staphylococcus aureus</i>	<i>Staphylococcus aureus</i> enterotoxin	Vomiting and diarrhoeal illness lasting < 24 hours
<i>Bacillus cereus</i>	Cereulide	Potent cytotoxin that destroys mitochondria. Causes a vomiting illness which may present within 4 hours of ingestion

Neurotoxins

Neurotoxins act on the nerves (tetanus) or the neuromuscular junction (botulism) causing

Neurotoxins

Neurotoxins act on the nerves (tetanus) or the neuromuscular junction (botulism) causing paralysis.

Organism	Toxin	Notes
<i>Clostridium tetani</i>	Tetanospasmin	Blocks the release of the inhibitory neurotransmitters GABA and glycine resulting in continuous motor neuron activity → continuous muscle contraction → lockjaw and respiratory paralysis
<i>Clostridium botulinum</i>	Botulinum toxin	Blocks acetylcholine (ACh) release leading to flaccid paralysis

Tissue invasive toxins

Organism	Toxin	Notes
<i>Clostridium perfringens</i>	α-toxin, a lecithinase	Causes gas gangrene (myonecrosis) and haemolysis
<i>Staphylococcus aureus</i>	Exfoliatin	Staphylococcal scalded skin syndrome

Miscellaneous toxins

Organism	Toxin	Notes
<i>Corynebacterium</i>	Diphtheria	ADP ribosylates elongation factor (EF-2), resulting in

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Staphylococcus aureus
Exfoliatin
Staphylococcal scalded skin syndrome

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Miscellaneous toxins

Organism	Toxin	Notes
<i>Corynebacterium diphtheriae</i>	Diphtheria toxin	ADP ribosylates elongation factor (EF-2), resulting in inhibition, causing a 'diphtheric membrane' on tonsils caused by necrotic mucosal cells. Systemic distribution may produce necrosis of myocardial, neural and renal tissue
<i>Pseudomonas aeruginosa</i>	Exotoxin A	Also inhibits EF-2 by the same mechanism as above
<i>Bacillus anthracis</i>	Oedema factor (EF)	Forms a calmodulin-dependent adenylate cyclase which increases cAMP, impairing the function of neutrophils/macrophages → reduced phagocytosis
<i>Bordetella pertussis</i>	Pertussis exotoxin	Inhibits G _i leading to increases in cAMP levels, impairing the function of neutrophils/macrophages → reduced phagocytosis

Endotoxins

Endotoxins are lipopolysaccharides that are released from Gram-negative bacteria such as *Neisseria meningitidis*.

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Acute phase proteins

Acute phase proteins

- CRP*
- procalcitonin
- ferritin
- fibrinogen
- alpha-1 antitrypsin
- caeruloplasmin
- serum amyloid A
- serum amyloid P component**
- haptoglobin
- complement

During the acute phase response the liver decreases the production of other proteins (sometimes referred to as negative acute phase proteins). Examples include:

- albumin
- transthyretin (formerly known as prealbumin)
- transferrin
- retinol binding protein
- cortisol binding protein

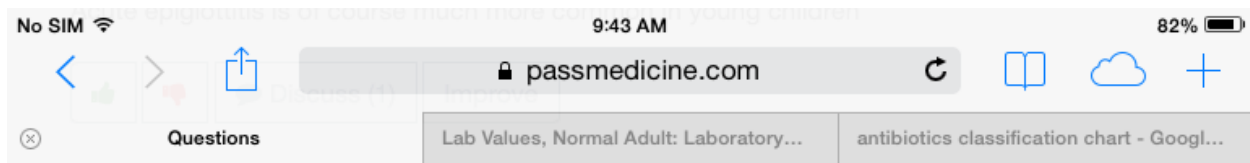
*Levels of CRP are commonly measured in acutely unwell patients. CRP is a protein synthesised in the liver and binds to phosphocholine in bacterial cells and on those cells undergoing apoptosis. In binding to these cells it is then able to activate the complement system. CRP levels are known to rise in patients following surgery. However, levels of greater than 150 at 48 hours post operatively are suggestive of evolving complications.

**plays a more significant role in other mammals such as mice

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Acute epiglottitis

Acute epiglottitis is rare but serious infection caused by *Haemophilus influenzae* type B. Prompt recognition and treatment is essential as airway obstruction may develop. Epiglottitis was generally considered a disease of childhood but in the UK it is now more common in adults due to the immunisation programme. The incidence of epiglottitis has decreased since the introduction of the Hib vaccine

Features

- rapid onset
- high temperature, generally unwell
- stridor
- drooling of saliva

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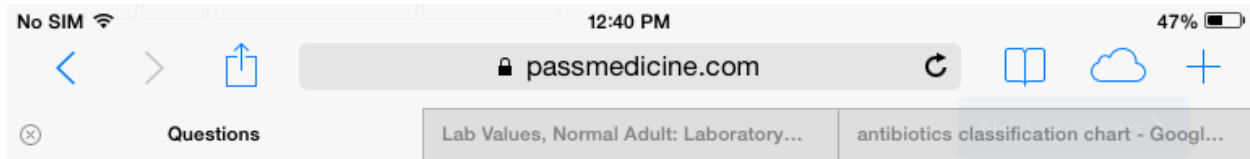
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Chickenpox

Chickenpox is caused by primary infection with varicella zoster virus. Shingles is reactivation of dormant virus in dorsal root ganglion

Chickenpox is highly infectious

- spread via the respiratory route
- can be caught from someone with shingles
- infectivity = 4 days before rash, until 5 days after the rash first appeared*
- incubation period = 10-21 days

Clinical features (tend to be more severe in older children/adults)

- fever initially
- itchy, rash starting on head/trunk before spreading. Initially macular then papular then vesicular
- systemic upset is usually mild

Management is supportive

- keep cool, trim nails
- calamine lotion
- school exclusion*: children should be kept away from school for at least 5 days from onset of rash (and not developing new lesions)
- immunocompromised patients and newborns with peripartum exposure should receive varicella zoster immunoglobulin (VZIG). If chickenpox develops then IV aciclovir should be considered

A common complication is secondary bacterial infection of the lesions. Rare complications include

- pneumonia
- encephalitis (cerebellar involvement may be seen)
- disseminated haemorrhagic chickenpox
- arthritis, nephritis and pancreatitis may very rarely be seen





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Chest x-ray showing miliary opacities secondary to healed varicella pneumonia. Multiple tiny calcific miliary opacities noted throughout both lungs. These are of uniform size and dense suggesting calcification. There is no focal lung parenchymal mass or cavitating lesion seen. The appearances are characteristic for healed varicella pneumonia.

*the official advice regarding school exclusion for chickenpox has gone back and forth over recent years. In September 2017 Public Health England advocated the 5 day rule:

Children should be kept away from school for at least 5 days from onset of rash (and not developing new lesions). It is not necessary for all the spots to have healed or crusted over before return to school as the risk of transmission to other children after 5 days is minimal.

<https://www.gov.uk/government/publications/health-protection-in-schools-and-other-childcare-facilities/chapter-9-managing-specific-infectious-diseases#chicken-pox-shingles>

Escherichia coli

Escherichia coli is a facultative anaerobic, lactose-fermenting, Gram negative rod which is a normal gut commensal.

E. coli infections lead to a variety of diseases in humans including:

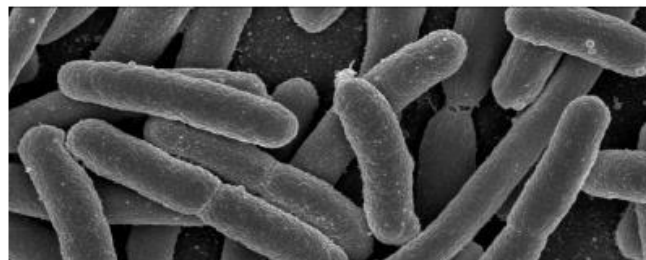
- diarrhoeal illnesses
- UTIs
- neonatal meningitis

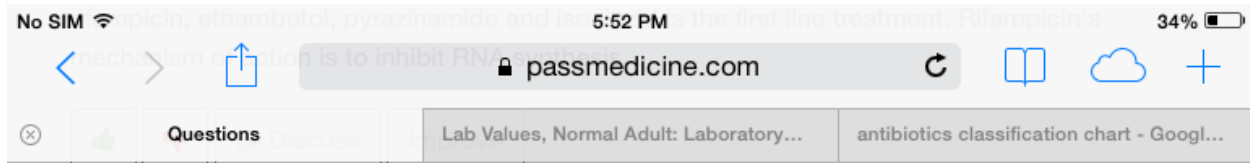
Serotypes

E. coli may be classified according to the antigens which may trigger an immune response:

Antigen	Origin	Notes
O	Lipopolysaccharide layer	
K	Capsule	Neonatal meningitis secondary to <i>E. coli</i> is usually caused by a serotype that contains the capsular antigen K-1
H	Flagellin	

E. coli O157:H7 is a particular strain associated with severe, haemorrhagic, watery diarrhoea. It has a high mortality rate and can be complicated by haemolytic uraemic syndrome. It is often spread by contaminated ground beef.





Next question >

Antibiotics: mechanism of action

The lists below summarise the site of action of the commonly used antibiotics

Inhibit cell wall formation

- penicillins
- cephalosporins

Inhibit protein synthesis

- aminoglycosides (cause misreading of mRNA)
- chloramphenicol
- macrolides (e.g. erythromycin)
- tetracyclines
- fusidic acid

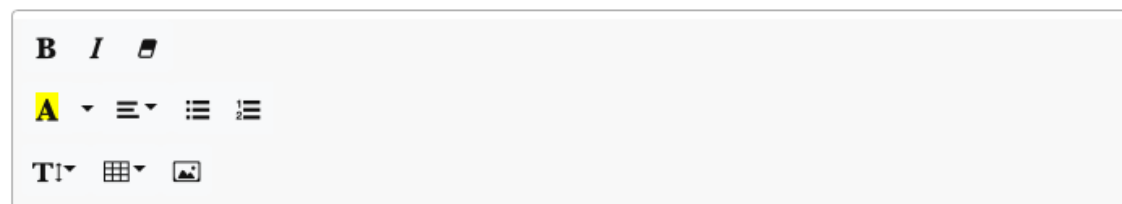
Inhibit DNA synthesis

- quinolones (e.g. ciprofloxacin)
- metronidazole
- sulphonamides
- trimethoprim

Inhibit RNA synthesis

- rifampicin

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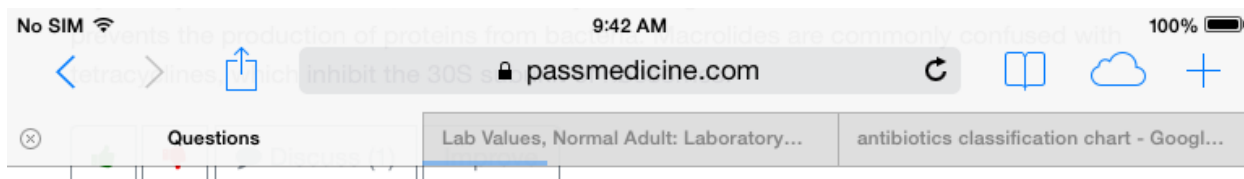


Antibiotics: protein synthesis inhibitors

Drug	Mechanism of action	Adverse effects	Notes
Aminoglycosides	Binds to 30S subunit causing misreading of mRNA	Nephrotoxicity, Ototoxicity	
Tetracyclines	Binds to 30S subunit blocking binding of aminoacyl-tRNA	Discolouration of teeth, photosensitivity	
Chloramphenicol	Binds to 50S subunit, inhibiting peptidyl transferase	Aplastic anaemia	
Clindamycin	Binds to 50S subunit, inhibiting translocation (movement of tRNA from acceptor site to peptidyl site)	Common cause of <i>C. difficile</i> diarrhoea	
Macrolides	Binds to 50S subunit, inhibiting translocation (movement of tRNA from acceptor site to peptidyl site)	Nausea (especially erythromycin), P450 inhibitor, prolonged QT interval	Commonly used for patients who are allergic to penicillin

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Post-splenectomy sepsis

Hyposplenism may complicate certain medical conditions where splenic atrophy occurs or may be the result of medical intervention such as splenic artery embolization and splenectomy for trauma. Diagnosis of hyposplenism is difficult and whilst there may be peripheral markers of the splenectomised state (e.g. Howell-Jolly bodies) these are neither 100% sensitive or specific. The most sensitive test is a radionucleotide labelled red cell scan.

Hyposplenism, by whatever mechanism it occurs dramatically increases the risk of post-splenectomy sepsis, particularly with encapsulated organisms. Since these organisms may be opsonised, but this then goes undetected at an immunological level due to loss of the spleen. For this reason, individuals are recommended to be vaccinated and have antibiotic prophylaxis.

Key recommendations

- All those with hyposplenism or may become so (such as prior to an elective splenectomy) should receive pneumococcal, Haemophilus type b and meningococcal type C vaccines. These should be administered 2 weeks prior to splenectomy or two weeks following splenectomy. The vaccine schedule for meningococcal disease essentially consists of a dose of Men C and Hib at 2 weeks and then a dose of the MenACWY vaccine one month later. Those aged under 2 may require a booster at 2 years. A dose of pneumococcal polyvalent polysaccharide vaccine (PPV) is given at two weeks. A conjugated vaccine (PCV) is offered to young children. The PCV is more immunogenic but covers fewer serotypes. Boosting PPV is either guided by serological measurements (where available) or by routine boosting doses at 5 yearly intervals.
- Annual influenza vaccination is recommended in all cases
- Antibiotic prophylaxis is offered to all. The risk of post-splenectomy sepsis is greatest immediately following splenectomy and in those aged less than 16 years or greater than 50 years. Individuals with a poor response to pneumococcal vaccination are another high-risk group. High-risk individuals should be counselled to take penicillin or macrolide prophylaxis. Those at low risk may choose to discontinue therapy. All patients should be advised about taking antibiotics early in the case of intercurrent infections.
- Asplenic individuals travelling to malaria endemic areas are at high risk and should have both pharmacological and mechanical protection.

Dosing

Questions asking about foramina of the skull have come up in the exam in previous years. Below is a brief summary of the major foramina, please see the Wikipedia link for a full list.

Foramen	Bone	Vessels	Nerves
Optic canal	Sphenoid	Ophthalmic artery	Optic nerve (II)
Superior orbital fissure	Sphenoid	Superior ophthalmic vein Inferior ophthalmic vein	Oculomotor nerve (III) Trochlear nerve (IV) lacrimal, frontal and nasociliary branches of ophthalmic nerve (V1) Abducent nerve (VI)
Inferior orbital fissure	Sphenoid and maxilla	Inferior ophthalmic veins Infraorbital artery Infraorbital vein	Zygomatic nerve and infraorbital nerve of maxillary nerve (V2) Orbital branches of pterygopalatine ganglion
Foramen rotundum	Sphenoid	-	Maxillary nerve (V2)
Foramen ovale	Sphenoid	Accessory meningeal artery	Mandibular nerve (V3)
Jugular foramen	Occipital and temporal	Posterior meningeal artery Ascending pharyngeal artery Inferior petrosal sinus Sigmoid sinus Internal jugular vein	Glossopharyngeal nerve (IX) Vagus nerve (X) Accessory nerve (XI)

Lower limb anatomy

The information below contains selected facts which commonly appear in examinations:

Nerve	Motor	Sensory	Typical mechanism of injury & notes
Femoral nerve	Knee extension, thigh flexion	Anterior and medial aspect of the thigh and lower leg	Hip and pelvic fractures Stab/gunshot wounds
Obturator nerve	Thigh adduction	Medial thigh	Anterior hip dislocation
Lateral cutaneous nerve of the thigh	None	Lateral and posterior surfaces of the thigh	Compression of the nerve near the ASIS → meralgia paraesthetica, a condition characterised by pain, tingling and numbness in the distribution of the lateral cutaneous nerve
Tibial nerve	Foot plantarflexion and inversion	Sole of foot	Not commonly injured as deep and well protected. Popliteal lacerations, posterior knee dislocation
Common peroneal nerve	Foot dorsiflexion and eversion Extensor hallucis longus	Dorsum of the foot and the lower lateral part of the leg	Injury often occurs at the neck of the fibula Tightly applied lower limb plaster cast Injury causes foot drop
Superior gluteal nerve	Hip abduction	None	Misplaced intramuscular injection Hip surgery Pelvic fracture Posterior hip dislocation Injury results in a positive Trendelenburg sign
Inferior gluteal nerve	Hip extension and lateral rotation	None	Generally injured in association with the sciatic nerve Injury results in difficulty rising from seated

Cranial nerves

The table below lists the major characteristics of the 12 cranial nerves:

Nerve	Functions	Clinical	Pathway/foramen
I (Olfactory)	Smell		Cribriform plate
II (Optic)	Sight		Optic canal
III (Oculomotor)	Eye movement (MR, IO, SR, IR) Pupil constriction Accommodation Eyelid opening	Palsy results in - ptosis 'down and out' eye - dilated, fixed pupil	Superior orbital fissure (SOF)
IV (Trochlear)	Eye movement (SO)	Palsy results in defective downward gaze → vertical diplopia	SOF
V (Trigeminal)	Facial sensation Mastication	Lesions may cause: - trigeminal neuralgia - loss of corneal reflex (afferent) - loss of facial sensation - paralysis of mastication muscles - deviation of jaw to weak side	V ₁ : SOF, V ₂ : Foramen rotundum, V ₃ : Foramen ovale
VI (Abducens)	Eye movement (LR)	Palsy results in defective abduction → horizontal diplopia	SOF
VII (Facial)	Facial movement Taste (anterior 2/3rds of tongue) Lacrimation Salivation	Lesions may result in: - flaccid paralysis of upper + lower face - loss of corneal reflex (efferent) - loss of taste - hyperacusis	Internal auditory meatus

VII (Facial)	Facial movement Taste (anterior 2/3rds of tongue) Lacrimation Salivation	Lesions may result in: - flaccid paralysis of upper + lower face - loss of corneal reflex (efferent) - loss of taste - hyperacusis	Internal auditory meatus
VIII (Vestibulocochlear)	Hearing, balance	Hearing loss Vertigo, nystagmus Acoustic neuromas are Schwann cell tumours of the cochlear nerve	Internal auditory meatus
IX (Glossopharyngeal)	Taste (posterior 1/3rd of tongue) Salivation Swallowing Mediates input from carotid body & sinus	Lesions may result in; - hypersensitive carotid sinus reflex - loss of gag reflex (afferent)	Jugular foramen
X (Vagus)	Phonation Swallowing Innervates viscera	Lesions may result in; - uvula deviates away from site of lesion - loss of gag reflex (efferent)	Jugular foramen
XI (Accessory)	Head and shoulder movement	Lesions may result in; weakness turning head to contralateral side	Jugular foramen
XII (Hypoglossal)	Tongue movement	Tongue deviates towards side of lesion	Hypoglossal canal

Some cranial nerves are motor, some sensory and some are both. The most useful mnemonic is given below.

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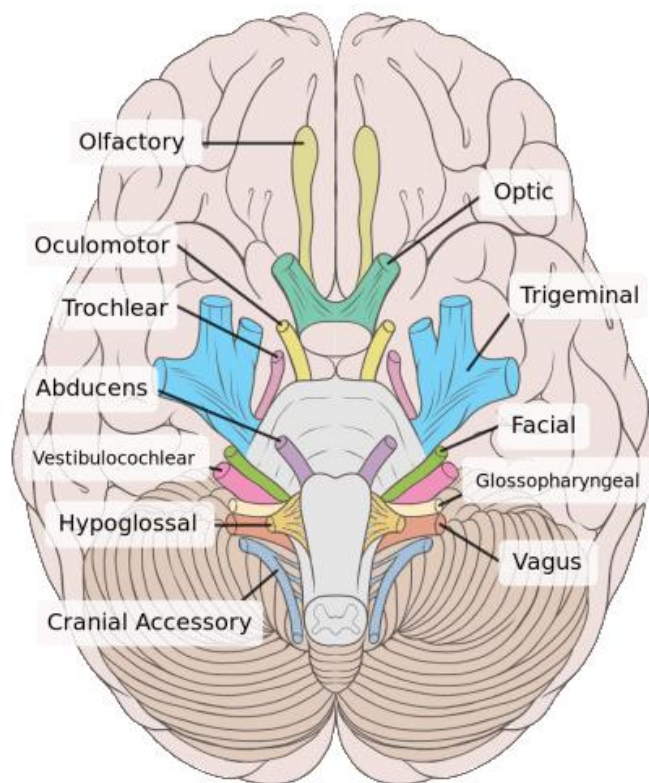
Some Say **M**arry **M**oney But My Brother Says **B**ig **B**rain **B**ig **B**rain **M**atter **M**ost**S** = Sensory, **M** = Motor, **B** = Both

Image sourced from Wikipedia

View from the inferior surface of the brain showing the emergence of the cranial nerves



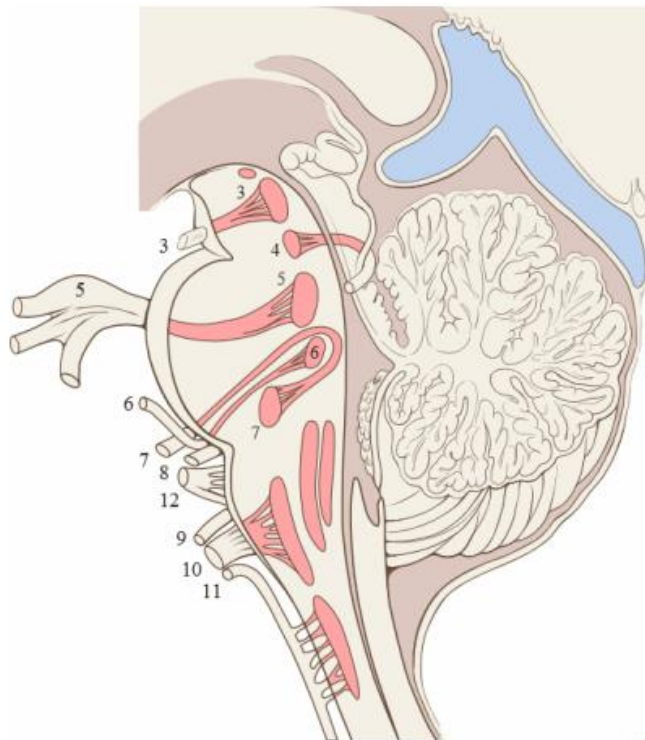


Image sourced from Wikipedia

Diagram showing the nuclei of the cranial nerves in the brainstem

Cranial nerve reflexes

Reflex	Afferent limb	Efferent limb
Corneal	Ophthalmic nerve (V ₁)	Facial nerve (VII)
Jaw jerk	Mandibular nerve (V ₃)	Mandibular nerve (V ₃)
Gag	Glossopharyngeal nerve (IX)	Vagal nerve (X)
Carotid sinus	Glossopharyngeal nerve (IX)	Vagal nerve (X)
Pupillary light	Optic nerve (II)	Oculomotor nerve (III)
Lacrimation	Ophthalmic nerve (V ₁)	Facial nerve (VII)

Dermatomes

The table below lists the major dermatome landmarks:

Nerve root	Landmark	Mnemonics
C2	Posterior half of the skull (cap)	
C3	High turtleneck shirt	
C4	Low-collar shirt	
C5	Ventral axial line of upper limb	
C6	Thumb + index finger	Make a 6 with your left hand by touching the tip of the thumb & index finger together - C6
C7	Middle finger + palm of hand	
C8	Ring + little finger	
T4	Nipples	T4 at the Teat Pore
T5	Inframammary fold	
T6	Xiphoid process	
T10	Umbilicus	BellybuT-TEN
L1	Inguinal ligament	L for ligament, 1 for 1nguinal
L4	Knee caps	



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Thumb + index finger

Make a 6 with your left hand by touching the tip of the thumb & index finger together - C6

C7

Middle finger + palm of hand

C8

Ring + little finger

T4

Nipples

T4 at the Teat Pore

T5

Inframammary fold

T6

Xiphoid process

T10

Umbilicus

BellybuT-TEN

L1

Inguinal ligament

L for ligament, 1 for 1nguinal

L4

Knee caps

Down on aLL fours - L4

L5

Big toe, dorsum of foot (except lateral aspect)

L5 = Largest of the 5 toes

S1

Lateral foot, small toe

S1 = the smallest one

S2,
S3

Genitalia

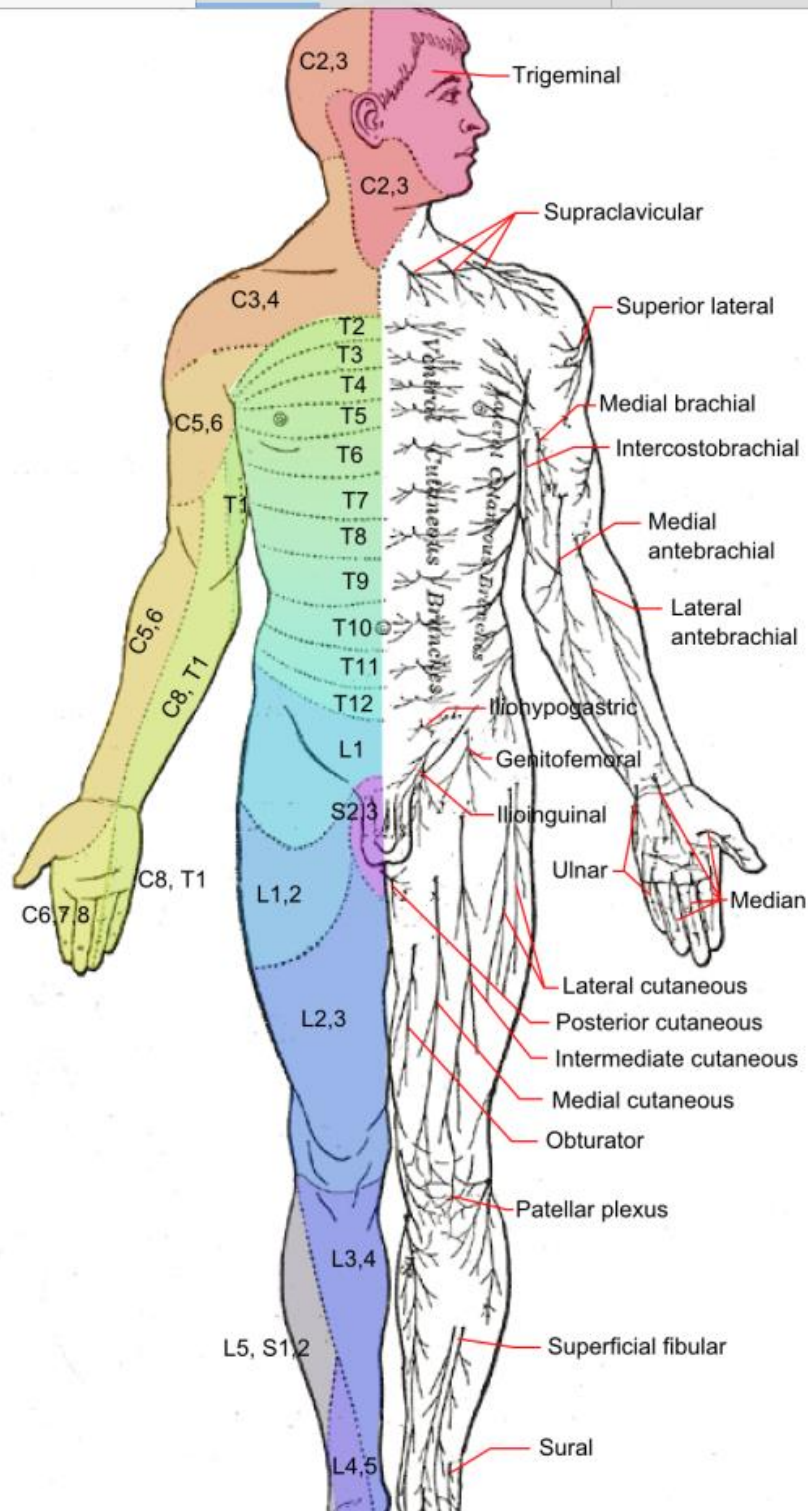
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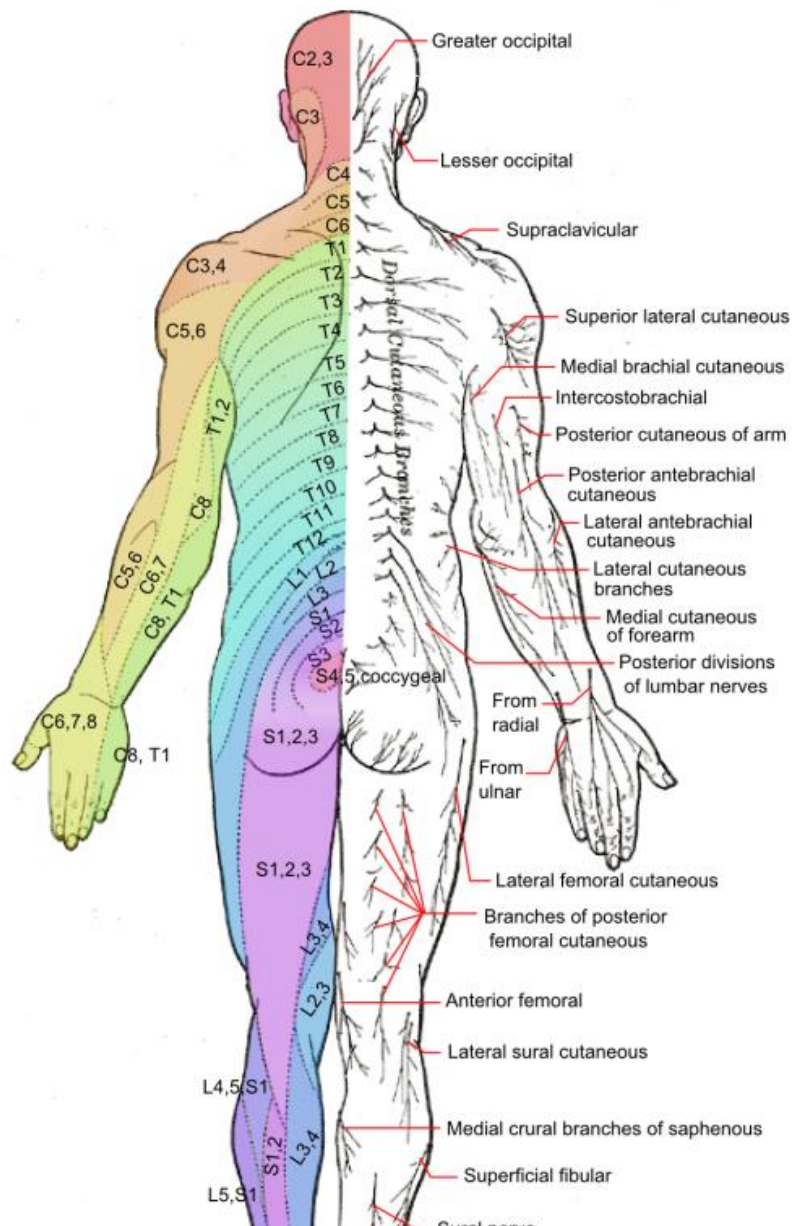
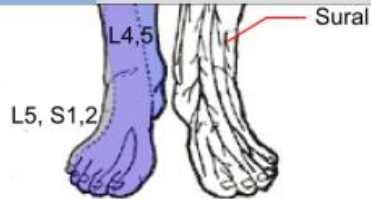
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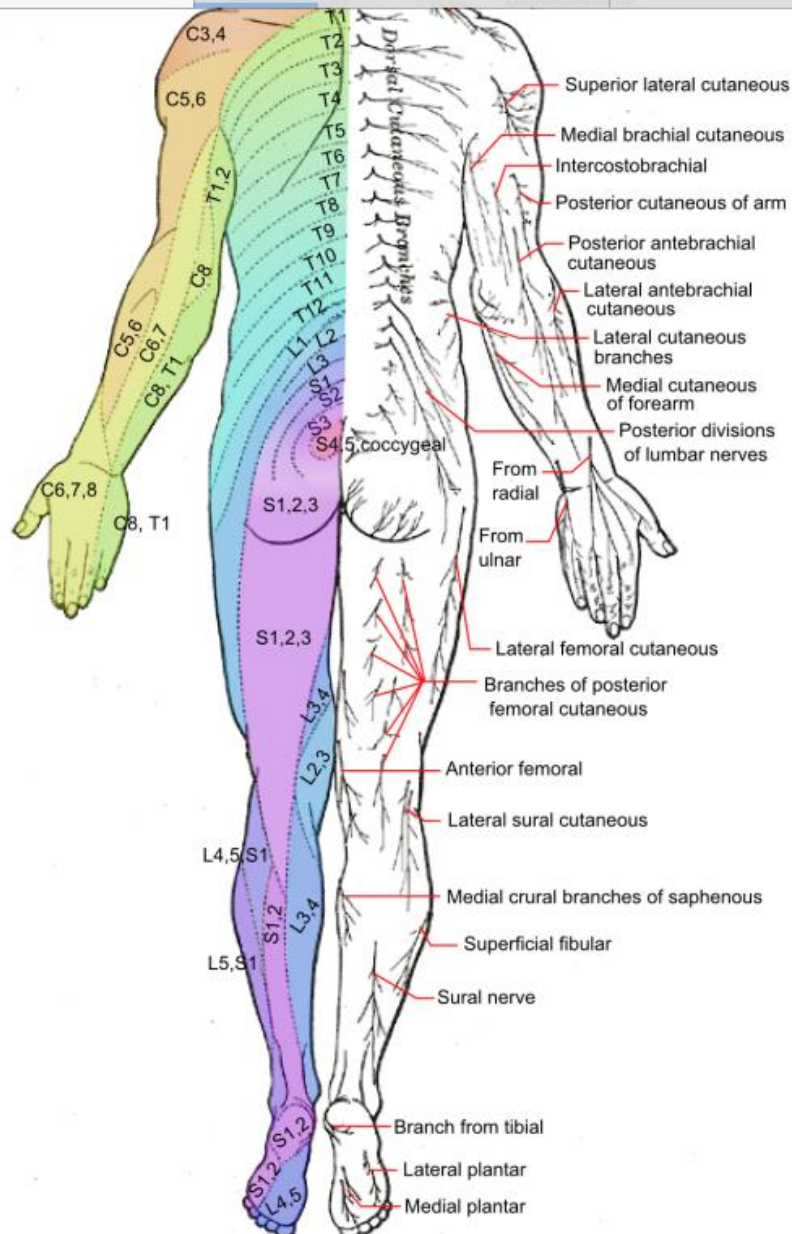
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Upper limb anatomy

The information below contains selected facts which commonly appear in examinations:

Nerve	Motor	Sensory	Typical mechanism of injury & notes
Musculocutaneous nerve (C5-C7)	Elbow flexion (supplies biceps brachii) and supination	Lateral part of the forearm	Isolated injury rare - usually injured as part of brachial plexus injury
Axillary nerve (C5,C6)	Shoulder abduction (deltoid muscle)	Inferior region of the deltoid muscle	Humeral neck fracture/dislocation Results in flattened deltoid
Radial nerve (C5-C8)	Extension (forearm, wrist, fingers, thumb)	Small area between the dorsal aspect of the 1st and 2nd metacarpals	Humeral midshaft fracture Palsy results in wrist drop
Median nerve (C6, C8, T1)	LOAF* muscles Features depend on the site of the lesion: - wrist: paralysis of thenar muscles, opponens pollicis - elbow: loss of pronation of forearm and weak wrist flexion	Palmar aspect of lateral 3½ fingers	Wrist lesion → carpal tunnel syndrome
Ulnar nerve (C8,	Intrinsic hand	Medial 1½ fingers	Medial epicondyle



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Ulnar nerve (C8, T1)	Intrinsic hand muscles except LOAF* Wrist flexion	Medial 1½ fingers	Medial epicondyle fracture Damage may result in a 'claw hand'
Long thoracic nerve (C5-C7)	Serratus anterior		Often during sport e.g. following a blow to the ribs. Also possible complication of mastectomy Damage results in a winged scapula

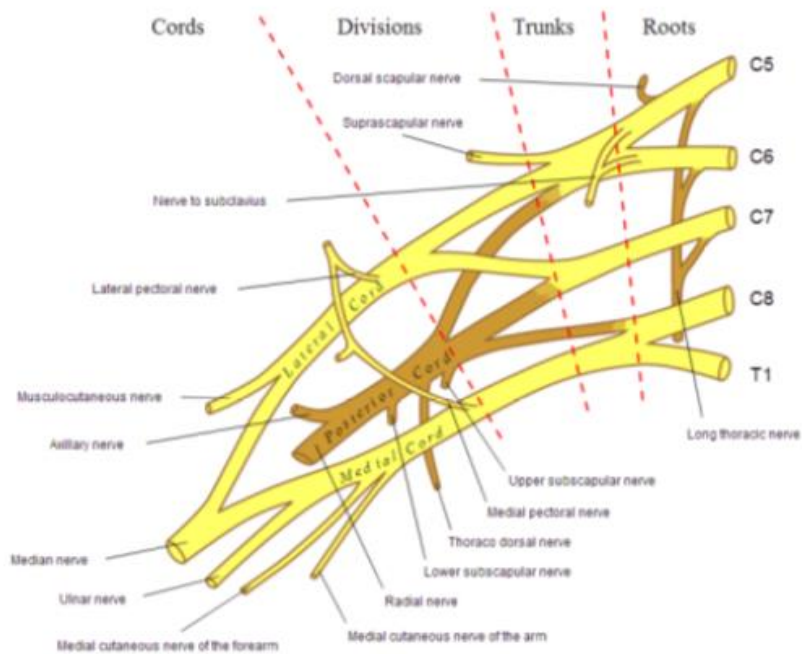


Diagram of the brachial plexus

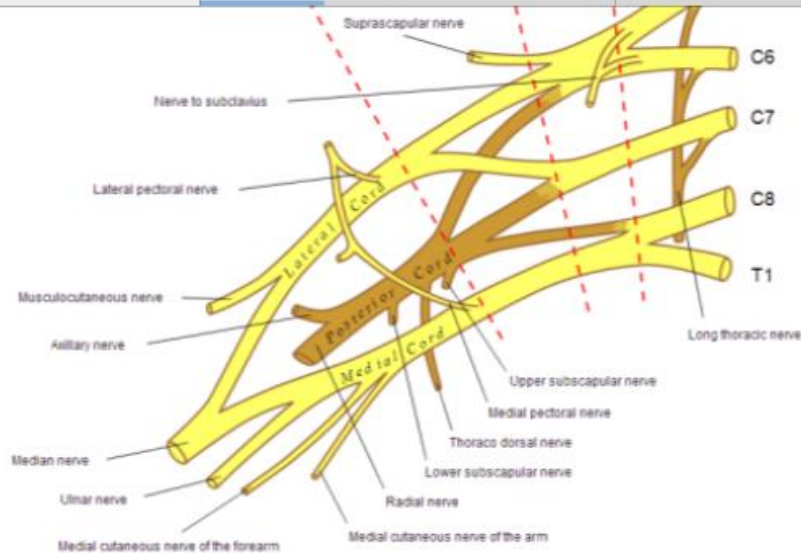


Diagram of the brachial plexus

Erb-Duchenne palsy ('waiter's tip')

- due to damage of the upper trunk of the brachial plexus (C5, C6)
- may be secondary to shoulder dystocia during birth
- the arm hangs by the side and is internally rotated, elbow extended

Klumpke injury

- due to damage of the lower trunk of the brachial plexus (C8, T1)
- as above, may be secondary to shoulder dystocia during birth. Also may be caused by a sudden upward jerk of the hand
- associated with Horner's syndrome

***LOAF muscles**

- Lateral two lumbricals
- Opponens pollicis
- Abductor pollicis brevis
- Flexor pollicis brevis

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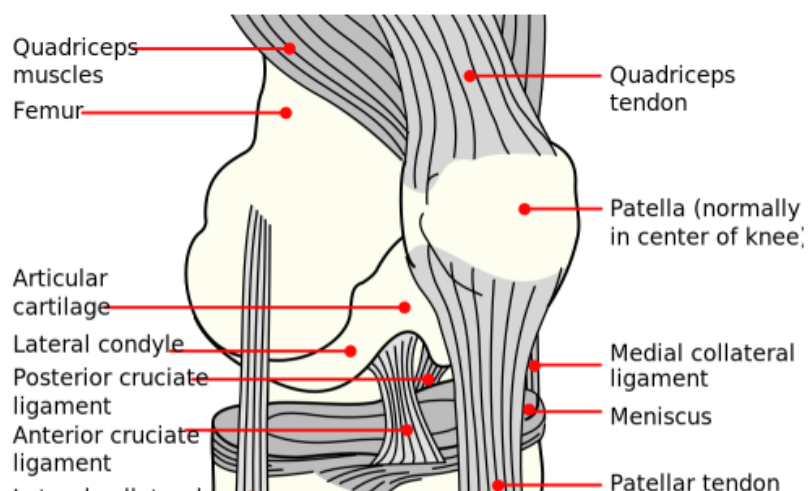
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Knee problems: children and young adults

The table below summarises the key features of common knee problems:

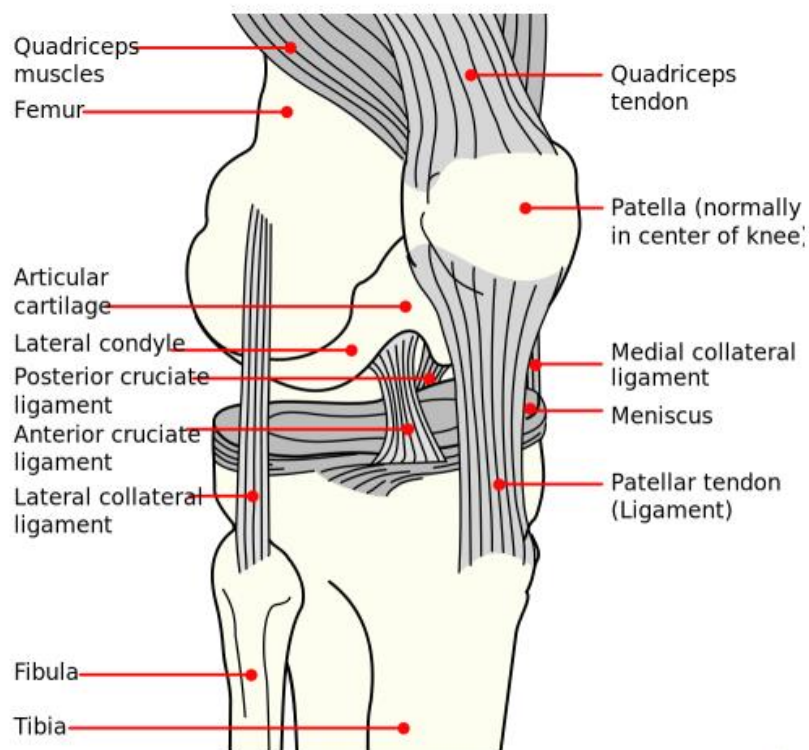
Condition	Key features
Chondromalacia patellae	Softening of the cartilage of the patella Common in teenage girls Characteristically anterior knee pain on walking up and down stairs and rising from prolonged sitting Usually responds to physiotherapy
Osgood-Schlatter disease (tibial apophysitis)	Seen in sporty teenagers Pain, tenderness and swelling over the tibial tubercle
Osteochondritis dissecans	Pain after exercise Intermittent swelling and locking
Patellar subluxation	Medial knee pain due to lateral subluxation of the patella Knee may give way
Patellar tendonitis	More common in athletic teenage boys Chronic anterior knee pain that worsens after running Tender below the patella on examination

Referred pain may come from hip problems such as slipped upper femoral epiphysis



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Patellar tendonitis	More common in athletic teenage boys Chronic anterior knee pain that worsens after running Tender below the patella on examination	

Referred pain may come from hip problems such as slipped upper femoral epiphysis



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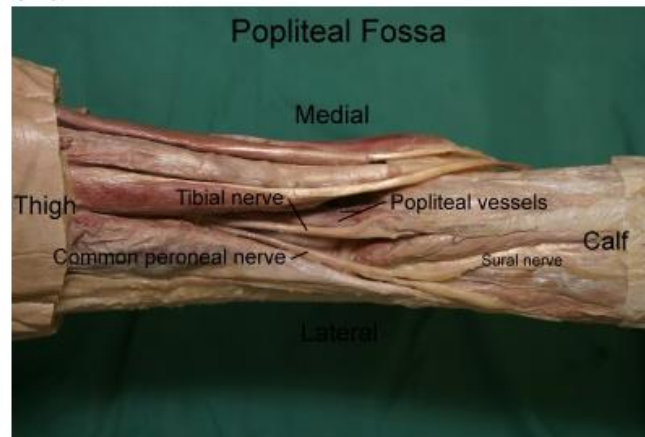
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Popliteal fossa

Boundaries of the popliteal fossa

Laterally	Biceps femoris above, lateral head of gastrocnemius and plantaris below
Medially	Semimembranosus and semitendinosus above, medial head of gastrocnemius below
Floor	Popliteal surface of the femur, posterior ligament of knee joint and popliteus muscle
Roof	Superficial and deep fascia

Image showing the popliteal fossa



Contents

- Popliteal artery and vein
- Small saphenous vein
- Common peroneal nerve
- Tibial nerve
- Posterior cutaneous nerve of the thigh
- Genicular branch of the obturator nerve
- Lymph nodes

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 Next question

Spinal cord

- Located in a canal within the vertebral column that affords it structural support.
 - Rostrally it continues to the medulla oblongata of the brain and caudally it tapers at a level corresponding to the L1-2 interspace (in the adult), a central structure, the filum terminale anchors the cord to the first coccygeal vertebra.
 - The spinal cord is characterised by cervico-lumbar enlargements and these, broadly speaking, are the sites which correspond to the brachial and lumbar plexuses respectively.

There are some key points to note when considering the surgical anatomy of the spinal cord:

- * During foetal growth the spinal cord becomes shorter than the spinal canal, hence the adult site of cord termination at the **L1-2 level**.
- * Due to growth of the vertebral column the spine segmental levels may not always correspond to bony landmarks as they do in the cervical spine.
- * The spinal cord is incompletely divided into two symmetrical halves by a **dorsal median sulcus** and **ventral median fissure**. Grey matter surrounds a central canal that is continuous rostrally with the ventricular system of the CNS.
- * The grey matter is sub divided cytoarchitecturally into **Rexeds laminae**.
- * Afferent fibres entering through the dorsal roots usually terminate near their point of entry but may travel for varying distances in **Lissauers tract**. In this way they may establish synaptic connections over several levels
- * At the tip of the dorsal horn are afferents associated with nociceptive stimuli. The ventral horn contains neurones that innervate skeletal muscle.

The key point to remember when revising CNS anatomy is to keep a clinical perspective in mind. So it is worth classifying the ways in which the spinal cord may become injured. These include:

- **Trauma** either direct or as a result of disc protrusion
- **Neoplasia** either by direct invasion (rare) or as a result of pathological vertebral fracture
- **Inflammatory diseases** such as Rheumatoid disease, or OA (formation of osteophytes

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- **Trauma** either direct or as a result of disc protrusion
- **Neoplasia** either by direct invasion (rare) or as a result of pathological vertebral fracture
- **Inflammatory diseases** such as Rheumatoid disease, or OA (formation of osteophytes compressing nerve roots etc.
- **Vascular** either as a result of stroke (rare in cord) or as complication of aortic dissection
- **Infection** historically diseases such as TB, epidural abscesses.

The anatomy of the cord will, to an extent dictate the clinical presentation. Some points/ conditions to remember:

- Brown- Sequard syndrome-Hemisecion of the cord producing ipsilateral loss of proprioception and upper motor neurone signs, plus contralateral loss of pain and temperature sensation. The explanation of this is that the fibres decussate at different levels.
- Lesions below L1 will tend to present with lower motor neurone signs

Next question >

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Radial nerve

Continuation of posterior cord of the brachial plexus (root values C5 to T1)

Path

- In the axilla: lies posterior to the axillary artery on subscapularis, latissimus dorsi and teres major.
- Enters the arm between the brachial artery and the long head of triceps (medial to humerus).
- Spirals around the posterior surface of the humerus in the groove for the radial nerve.
- At the distal third of the lateral border of the humerus it then pierces the intermuscular septum and descends in front of the lateral epicondyle.
- At the lateral epicondyle it lies deeply between brachialis and brachioradialis where it then divides into a superficial and deep terminal branch.
- Deep branch crosses the supinator to become the posterior interosseous nerve.

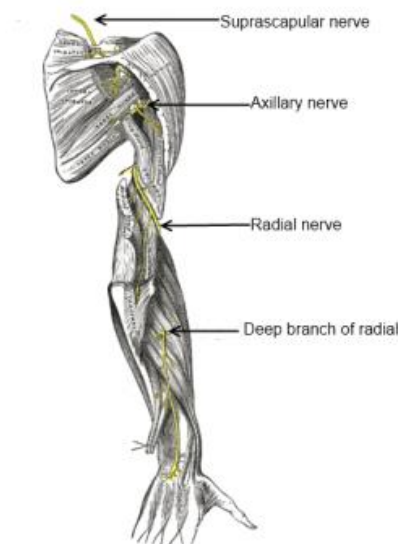


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In the image above the relationships of the radial nerve can be appreciated

Regions innervated

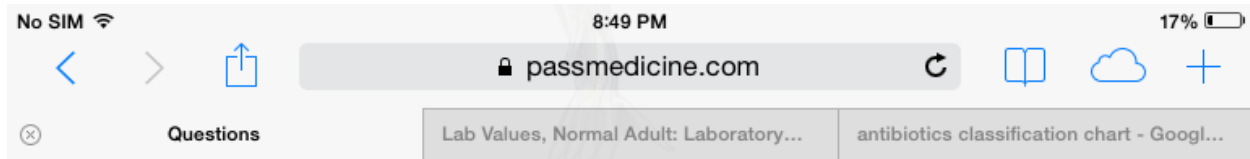


Image sourced from Wikipedia

In the image above the relationships of the radial nerve can be appreciated

Regions innervated

Motor (main nerve)	• Triceps • Anconeus • Brachioradialis • Extensor carpi radialis
Motor (posterior interosseous branch)	• Supinator • Extensor carpi ulnaris • Extensor digitorum • Extensor indicis • Extensor digiti minimi • Extensor pollicis longus and brevis • Abductor pollicis longus
Sensory	The area of skin supplying the proximal phalanges on the dorsal aspect of the hand is supplied by the radial nerve (this does not apply to the little finger and part of the ring finger)

Muscular innervation and effect of denervation

Anatomical location	Muscle affected	Effect of paralysis
Shoulder	Long head of triceps	Minor effects on shoulder stability in abduction
Arm	Triceps	Loss of elbow extension
Forearm	Supinator Brachioradialis Extensor carpi radialis	Weakening of supination of prone hand and elbow flexion in mid prone position

Muscular innervation and effect of denervation

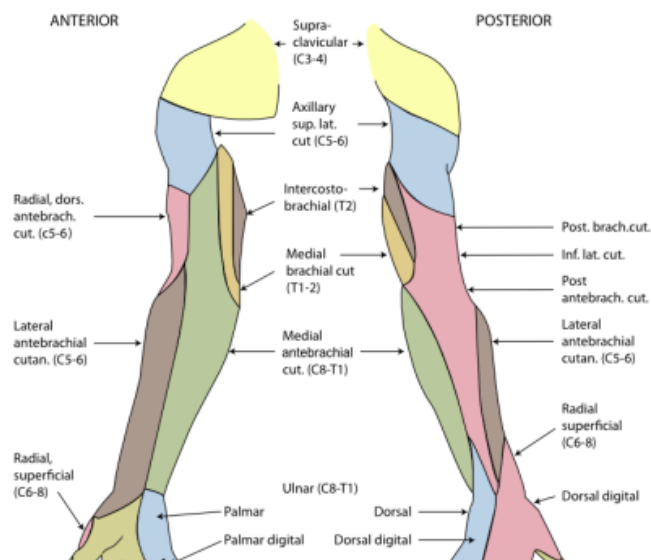
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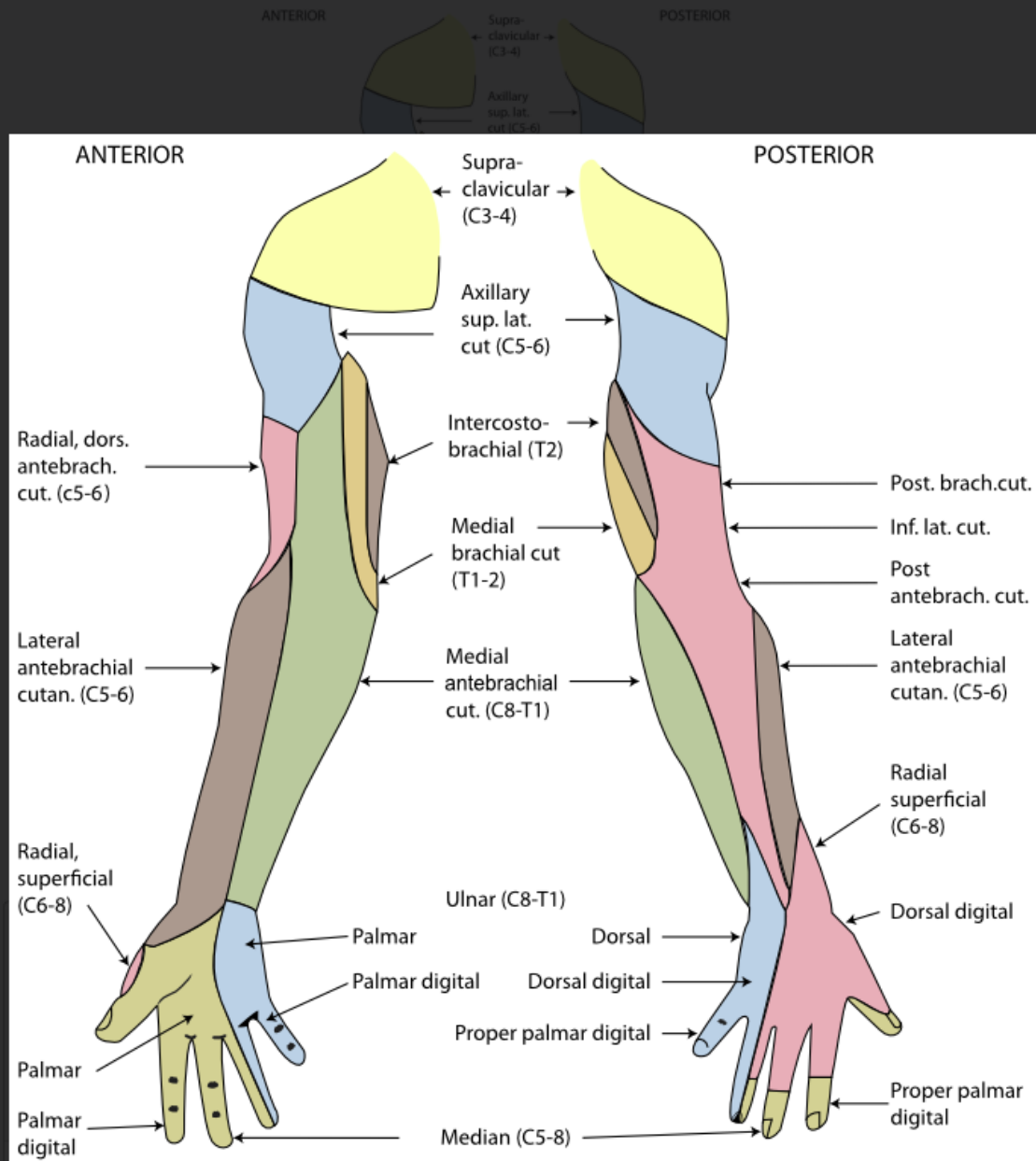
Patterns of damage

- wrist drop
- sensory loss to small area between the dorsal aspect of the 1st and 2nd metacarpals

Axillary damage

- as above
- paralysis of triceps





Dermatomes

The table below lists the major dermatome landmarks:

Nerve root	Landmark	Mnemonics
C2	Posterior half of the skull (cap)	
C3	High turtleneck shirt	
C4	Low-collar shirt	
C5	Ventral axial line of upper limb	
C6	Thumb + index finger	Make a 6 with your left hand by touching the tip of the thumb & index finger together - C6
C7	Middle finger + palm of hand	
C8	Ring + little finger	
T4	Nipples	T4 at the Teat Pore
T5	Inframammary fold	
T6	Xiphoid process	
T10	Umbilicus	BellybuT-TEN

C7	Middle finger + palm of hand	
C8	Ring + little finger	
T4	Nipples	T4 at the Teat Pore
T5	Inframammary fold	
T6	Xiphoid process	
T10	Umbilicus	BellybuT-TEN
L1	Inguinal ligament	L for ligament, 1 for 1nguinal
L4	Knee caps	Down on aLL fours - L4
L5	Big toe, dorsum of foot (except lateral aspect)	L5 = Largest of the 5 toes
S1	Lateral foot, small toe	S1 = the smallest one
S2, S3	Genitalia	

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Next question >

Familial hypercholesterolaemia

Familial hypercholesterolaemia (FH) is an autosomal dominant condition that is thought to affect around 1 in 500 people. It results in high levels of LDL-cholesterol which, if untreated, may cause early cardiovascular disease (CVD). FH is caused by mutations in the gene which encodes the LDL-receptor protein.

Clinical diagnosis is now based on the **Simon Broome criteria**:

- in adults total cholesterol (TC) > 7.5 mmol/l and LDL-C > 4.9 mmol/l or children TC > 6.7 mmol/l and LDL-C > 4.0 mmol/l, plus:
- for definite FH: tendon xanthoma in patients or 1st or 2nd degree relatives or DNA-based evidence of FH
- for possible FH: family history of myocardial infarction below age 50 years in 2nd degree relative, below age 60 in 1st degree relative, or a family history of raised cholesterol levels

Management

- the use of CVD risk estimation using standard tables is not appropriate in FH as they do not accurately reflect the risk of CVD
- referral to a specialist lipid clinic is usually required
- the maximum dose of potent statins are usually required
- first-degree relatives have a 50% chance of having the disorder and should therefore be offered screening. This includes children who should be screened by the age of 10 years if there is one affected parent
- statins should be discontinued in women 3 months before conception due to the risk of congenital defects

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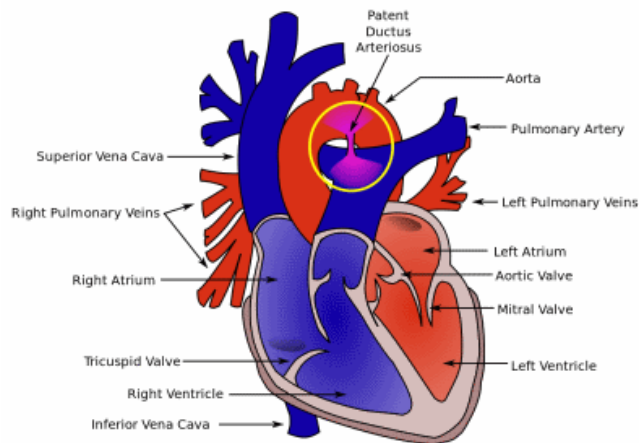


Patent ductus arteriosus



Overview

- a form of congenital heart defect
- generally classed as 'acyanotic'. However, uncorrected can eventually result in late cyanosis in the lower extremities, termed differential cyanosis.
- connection between the pulmonary trunk and descending aorta
- more common in premature babies, born at high altitude or maternal rubella infection in the first trimester



Features

- left subclavicular thrill
- continuous 'machinery' murmur
- large volume, bounding, collapsing pulse
- wide pulse pressure
- heaving apex beat

Management

- indomethacin closes the connection in the majority of cases
- if associated with another congenital heart defect amenable to surgery then prostaglandin E1 is useful to keep the duct open until after surgical repair

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Cardiac action potential

Cardiac action potential

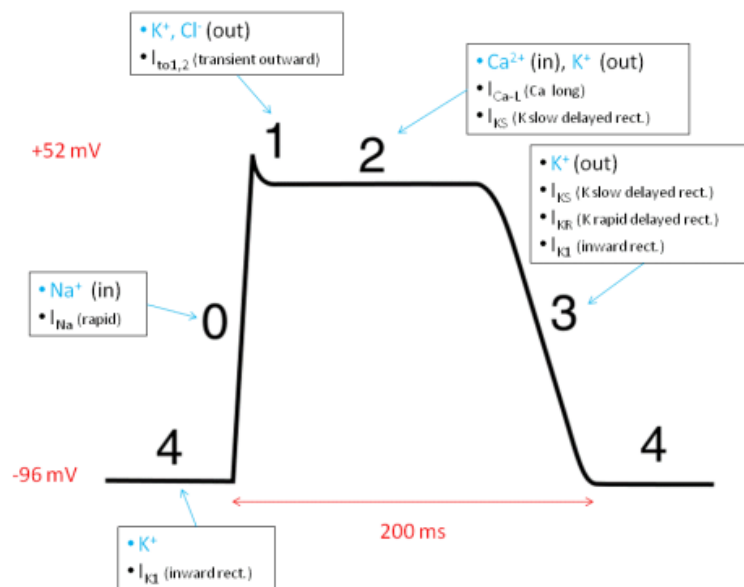


Image sourced from Wikipedia

Phase	Description	Mechanism
0	Rapid depolarisation	Rapid sodium influx These channels automatically deactivate after a few ms
1	Early repolarisation	Efflux of potassium
2	Plateau	Slow influx of calcium
3	Final repolarisation	Efflux of potassium
4	Restoration of ionic concentrations	Resting potential is restored by Na^+/K^+ ATPase There is slow entry of Na^+ into the cell decreasing the potential difference until the threshold potential is reached, triggering a new action potential

NB cardiac muscle remains contracted 10-15 times longer than skeletal muscle

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NB cardiac muscle remains contracted 10-15 times longer than skeletal muscle

Conduction velocity

Site	Speed
Atrial conduction	Spreads along ordinary atrial myocardial fibres at 1 m/sec
AV node conduction	0.05 m/sec
Ventricular conduction	Purkinje fibres are of large diameter and achieve velocities of 2-4 m/sec (this allows a rapid and coordinated contraction of the ventricles)














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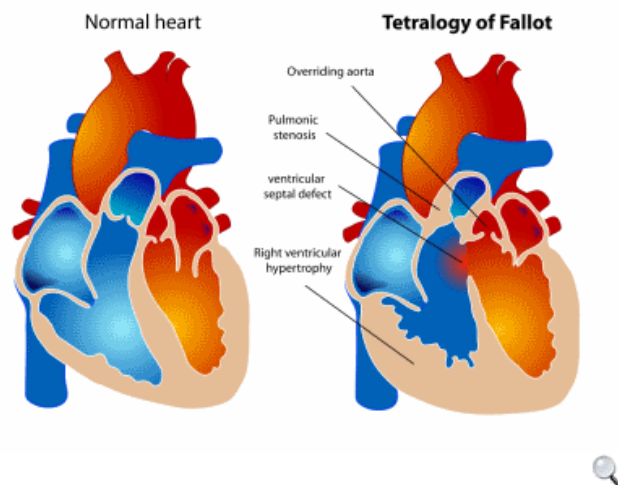
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Tetralogy of Fallot

Tetralogy of Fallot (TOF) is the most common cause of cyanotic congenital heart disease*. It typically presents at around 1-2 months, although may not be picked up until the baby is 6 months old

TOF is a result of anterior malalignment of the aorticopulmonary septum. The four characteristic features are:

- ventricular septal defect (VSD)
- right ventricular hypertrophy
- right ventricular outflow tract obstruction, pulmonary stenosis
- overriding aorta



The severity of the right ventricular outflow tract obstruction determines the degree of cyanosis and clinical severity

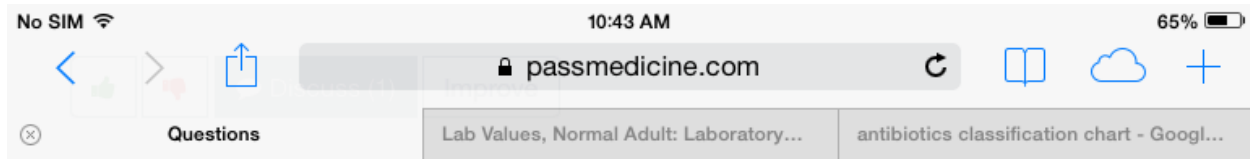
Other features

- cyanosis
- causes a right-to-left shunt
- ejection systolic murmur due to pulmonary stenosis (the VSD doesn't usually cause a murmur)
- a right-sided aortic arch is seen in 25% of patients
- chest x-ray shows a 'boot-shaped' heart, ECG shows right ventricular hypertrophy

Management

- surgical repair is often undertaken in two parts
- cyanotic episodes may be helped by beta-blockers to reduce infundibular spasm

*however, at birth transposition of the great arteries is the more common lesion as patients with TOF generally present at around 1-2 months



Ebstein's anomaly

Ebstein's anomaly is a congenital heart defect characterised by low insertion of the tricuspid valve resulting in a large atrium and small ventricle. It is sometimes referred to as 'atrialisation' of the right ventricle.

Associations

- tricuspid incompetence (pan-systolic murmur, giant V waves in JVP)
- Wolff-Parkinson White syndrome

Ebstein's anomaly may be caused by exposure to lithium in-utero

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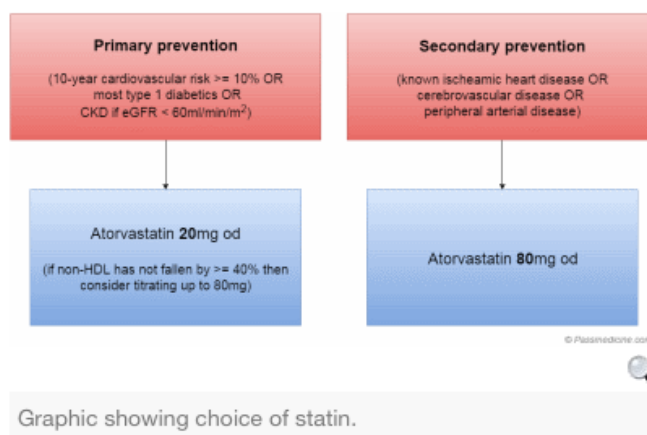
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[Google search on "Ebstein's anomaly"](#)

Hyperlipidaemia: management

In 2014 NICE updated their guidelines on lipid modification. This proved highly controversial as it meant that we should be recommending statins to a significant proportion of the population over the age of 60 years. Anyway, the key points of the new guidelines are summarised below.



Primary prevention - who and how to assess risk

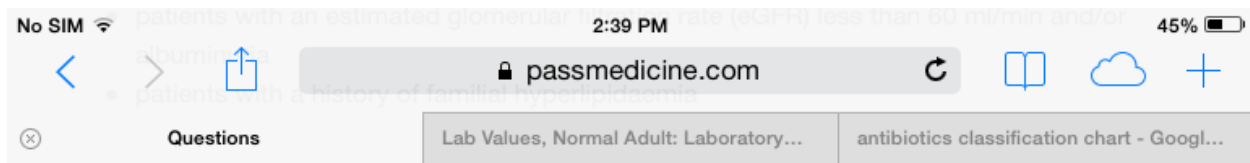
A systematic strategy should be used to identify people aged over 40 years who are likely to be at high risk of cardiovascular disease (CVD), defined as a 10-year risk of **10%** or greater.

NICE recommend we use the **QRISK2** CVD risk assessment tool for patients aged ≤ 84 years. Patients ≥ 85 years are at high risk of CVD due to their age. QRISK2 should not be used in the following situations as there are more specific guidelines for these patient groups:

- type 1 diabetics
- patients with an estimated glomerular filtration rate (eGFR) less than 60 ml/min and/or albuminuria
- patients with a history of familial hyperlipidaemia

NICE suggest QRISK2 may underestimate CVD risk in the following population groups:

- people treated for HIV
- people with serious mental health problems
- people taking medicines that can cause dyslipidaemia such as antipsychotics, corticosteroids or immunosuppressant drugs



NICE suggest QRISK2 may underestimate CVD risk in the following population groups:

- people treated for HIV
- people with serious mental health problems
- people taking medicines that can cause dyslipidaemia such as antipsychotics, corticosteroids or immunosuppressant drugs
- people with autoimmune disorders/systemic inflammatory disorders such as systemic lupus erythematosus

Measuring lipid levels

When measuring lipids both the total cholesterol and HDL should be checked to provide the most accurate risk of CVD. A full lipid profile should also be checked (i.e. including triglycerides) before starting a statin. The samples does not need to be fasting.

In the vast majority of patient the cholesterol measurements will be fed into the QRISK2 tool. If however the patient's cholesterol is very high we should consider familial hyperlipidaemia. NICE recommend the following that we should consider the possibility of familial hypercholesterolaemia and investigate further if the total cholesterol concentration is > 7.5 mmol/l and there is a family history of premature coronary heart disease. They also recommend referring people with a total cholesterol > 9.0 mmol/l or a non-HDL cholesterol (i.e. LDL) of > 7.5 mmol/l even in the absence of a first-degree family history of premature coronary heart disease.

Interpreting the QRISK2 result

Probably the headline changes in the 2014 guidelines was the new, lower cut-off of 10-year CVD risk cut-off of 10%.

NICE now recommend we offer a statin to people with a QRISK2 10-year risk of $\geq 10\%$

Lifestyle factors are of course important and NICE recommend that we give patients the option of having their CVD risk reassessed after a period of time before starting a statin.

Atorvastatin 20mg should be offered first-line.

Special situations

Special situations

Type 1 diabetes mellitus

- NICE recommend that we 'consider statin treatment for the primary prevention of CVD in all adults with type 1 diabetes'
- atorvastatin 20 mg should be offered if type 1 diabetics who are:
 - → older than 40 years, or
 - → have had diabetes for more than 10 years or
 - → have established nephropathy or
 - → have other CVD risk factors

Chronic kidney disease (CKD)

- atorvastatin 20mg should be offered to patients with CKD
- increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved and the eGFR > 30 ml/min. If the eGFR is < 30 ml/min a renal specialist should be consulted before increasing the dose

Secondary prevention

All patients with CVD should be taking a statin in the absence of any contraindication.

Atorvastatin 80mg should be offered first-line.

Follow-up of people started on statins

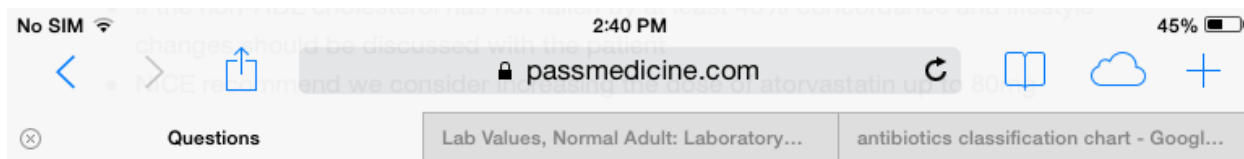
NICE recommend we follow-up patients at 3 months

- repeat a full lipid profile
- if the non-HDL cholesterol has not fallen by at least 40% concordance and lifestyle changes should be discussed with the patient
- NICE recommend we consider increasing the dose of atorvastatin up to 80mg

Lifestyle modifications

These are in many ways predictable but NICE make a number of specific points:

Cardioprotective diet



Lifestyle modifications

These are in many ways predictable but NICE make a number of specific points:

Cardioprotective diet

- total fat intake should be $\leq 30\%$ of total energy intake
- saturated fats should be $\leq 7\%$ of total energy intake
- intake of dietary cholesterol should be < 300 mg/day
- saturated fats should be replaced by monounsaturated and polyunsaturated fats where possible
- replace saturated and monounsaturated fat intake with olive oil, rapeseed oil or spreads based on these oils
- choose wholegrain varieties of starchy food
- reduce their intake of sugar and food products containing refined sugars including fructose
- eat at least 5 portions of fruit and vegetables per day
- eat at least 2 portions of fish per week, including a portion of oily fish
- eat at least 4 to 5 portions of unsalted nuts, seeds and legumes per week

Physical activity

- each week aim for at least 150 minutes of moderate intensity aerobic activity or 75 minutes of vigorous intensity aerobic activity or a mix of moderate and vigorous aerobic activity
- do musclestrengthening activities on 2 or more days a week that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders and arms) in line with national guidance for the general population

Weight management

- no specific advice is given, overweight patients should be managed in keeping with relevant NICE guidance

Alcohol intake

- again no specific advice, other than the general recommendation that males drink no more than 3-4 units/day and females no more than 2-3 units/day

Smoking cessation

- smokers should be encouraged to quit
-

Next question >

Iron metabolism

Absorption

- upper small intestine
- about 10% of dietary iron absorbed
- Fe^{2+} (ferrous iron) much better absorbed than Fe^{3+} (ferric iron)
- absorption is regulated according to body's need
- increased by vitamin C, gastric acid
- decreased by proton pump inhibitors, tetracycline, gastric achlorhydria, tannin (found in tea)

Distribution in body

- total body iron = 4g
- haemoglobin = 70%
- ferritin and haemosiderin = 25%
- myoglobin = 4%
- plasma iron = 0.1%

Transport

- carried in plasma as Fe^{3+} bound to transferrin

Storage

- stored as ferritin in tissues

Excretion

- lost via intestinal tract following desquamation

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Atherosclerosis

Atherosclerosis is a complex process which develops over a number of years. A number of changes can be seen:

- initial endothelial dysfunction is triggered by a number of factors such as smoking, hypertension and hyperglycaemia
- this results in a number of changes to the endothelium including pro-inflammatory, pro-oxidant, proliferative and reduced nitric oxide bioavailability
- fatty infiltration of the subendothelial space by low-density lipoprotein (LDL) particles
- monocytes migrate from the blood and differentiate into macrophages. These macrophages then phagocytose oxidized LDL, slowly turning into large 'foam cells'. As these macrophages die the result can further propagate the inflammatory process.
- smooth muscle proliferation and migration from the tunica media into the intima results in formation of a fibrous capsule covering the fatty plaque.

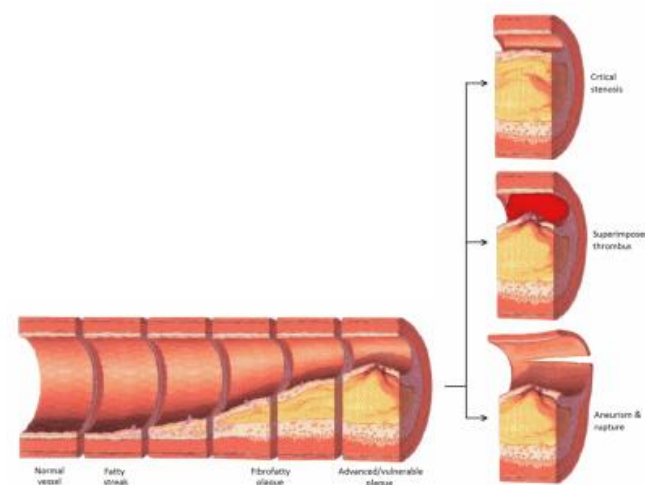


Image sourced from Wikipedia

Diagram showing the progression of atherosclerosis in the coronary arteries with associated complications on the right.



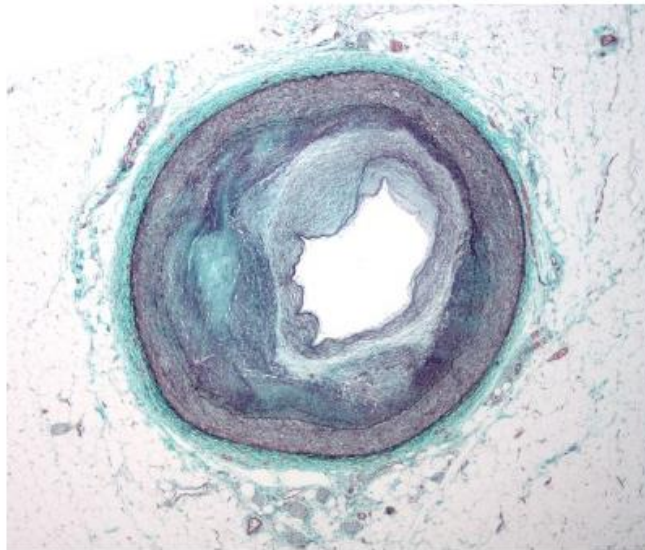


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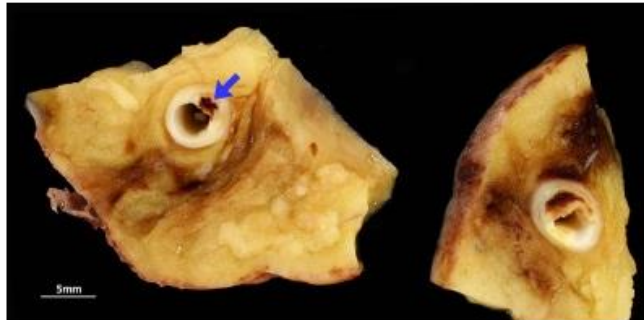
Slide showing a markedly narrowed coronary artery secondary to atherosclerosis. Stained with Masson's trichrome.

Complications of atherosclerosis

Taking the coronary arteries as an example, once a plaque has formed a number of complications can develop:

- the plaque forms a physical blockage in the lumen of the coronary artery. This may cause reduced blood flow and hence oxygen to the myocardium, particularly at times of increased demand, resulting clinically in angina
- the plaque may rupture, potentially causing a complete occlusion of the coronary artery. This may result in a myocardial infarction





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Ruptured coronary artery plaque resulting in thrombosis and associated myocardial infarction.



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Pathological specimen showing infarction of the anteroseptal and lateral wall of the left ventricle. There is a background of biventricular myocardial hypertrophy.

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Atrial natriuretic peptide

Basics

- secreted mainly from myocytes of right atrium and ventricle in response to increased blood volume
- secreted by both the right and left atria (right >> left)
- 28 amino acid peptide hormone, which acts via cGMP
- degraded by endopeptidases

Actions

- natriuretic, i.e. promotes excretion of sodium
- lowers BP
- antagonises actions of angiotensin II, aldosterone

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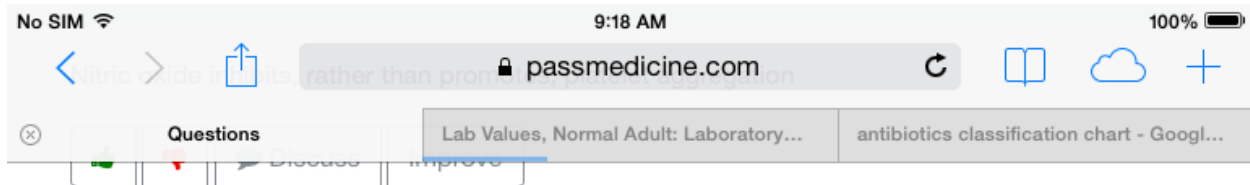
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Nitric oxide

Previously known as endothelium derived relaxation factor, nitric oxide (NO) has emerged as a molecule which is integral to many physiological and pathological processes. It is formed from L-arginine and oxygen by nitric oxide synthetase (NOS). An inducible form of NOS has been shown to be present in macrophages. Nitric oxide has a very short half-life (seconds), being inactivated by oxygen free radicals

Effects

- acts on guanylate cyclase leading to raised intracellular cGMP levels and therefore decreasing Ca^{2+} levels
- vasodilation, mainly venodilation
- inhibits platelet aggregation

Clinical relevance

- underproduction of NO is implicated in hypertrophic pyloric stenosis
- lack of NO is thought to promote atherosclerosis
- in sepsis increased levels of NO contribute to septic shock
- organic nitrates (metabolism produces NO) is widely used to treat cardiovascular disease (e.g. angina, heart failure)
- sildenafil is thought to potentiate the action of NO on penile smooth muscle and is used in the treatment of erectile dysfunctions

Next question >



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Questions Lab Values, Normal Adult: Laboratory... antibiotics classification chart - Googl...

End systolic LV volume - end diastolic LV volume 12%

Stroke volume / end diastolic LV volume 49%



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Cardiovascular physiology

Left ventricular ejection fraction

Left ventricular ejection fraction = (stroke volume / end diastolic LV volume) * 100%

Stroke volume = end diastolic LV volume - end systolic LV volume

Pulse pressure

Pulse pressure = Systolic Pressure - Diastolic Pressure

Factors which increase pulse pressure

- a less compliant aorta (this tends to occur with advancing age)
- increased stroke volume

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Disseminated intravascular coagulation

Simultaneous coagulation and haemorrhage caused by initially formation of thrombi which consume clotting factors (factors 5,8) and platelets, ultimately leading to bleeding

Causes include:

- Infection
- Malignancy
- Trauma e.g. major surgery, burns, shock, dissecting aortic aneurysm
- Liver disease
- Obstetric complications

Key points

- Clinically bleeding is usually a dominant feature, bruising, ischaemia and organ failure
- Blood tests: prolonged clotting times, thrombocytopenia, decreased fibrinogen, increased fibrinogen degradation products
- Treat the underlying cause and supportive management

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Familial hypercholesterolaemia

Familial hypercholesterolaemia (FH) is an autosomal dominant condition that is thought to affect around 1 in 500 people. It results in high levels of LDL-cholesterol which, if untreated, may cause early cardiovascular disease (CVD). FH is caused by mutations in the gene which encodes the LDL-receptor protein.

Clinical diagnosis is now based on the **Simon Broome criteria**:

- in adults total cholesterol (TC) > 7.5 mmol/l and LDL-C > 4.9 mmol/l or children TC > 6.7 mmol/l and LDL-C > 4.0 mmol/l, plus:
- for definite FH: tendon xanthoma in patients or 1st or 2nd degree relatives or DNA-based evidence of FH
- for possible FH: family history of myocardial infarction below age 50 years in 2nd degree relative, below age 60 in 1st degree relative, or a family history of raised cholesterol levels

Management

- the use of CVD risk estimation using standard tables is not appropriate in FH as they do not accurately reflect the risk of CVD
- referral to a specialist lipid clinic is usually required
- the maximum dose of potent statins are usually required
- first-degree relatives have a 50% chance of having the disorder and should therefore be offered screening. This includes children who should be screened by the age of 10 years if there is one affected parent
- statins should be discontinued in women 3 months before conception due to the risk of congenital defects

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cholestasis, hypothyroidism



Next question >

Hyperlipidaemia: secondary causes

Causes of predominantly hypertriglyceridaemia

- diabetes mellitus (types 1 and 2)
- obesity
- alcohol
- chronic renal failure
- drugs: thiazides, non-selective beta-blockers, unopposed oestrogen
- liver disease

Causes of predominantly hypercholesterolaemia

- nephrotic syndrome
- cholestasis
- hypothyroidism

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Macrophages 5%

Elastocytes 4%



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Pulmonary surfactant

Surfactant is a mixture of phospholipids, carbohydrates and proteins released by type 2 pneumocytes. The main functioning component is dipalmitoyl phosphatidylcholine (DPPC) which reduces alveolar surface tension.

Basics

- first detectable around 28 weeks
- as alveoli decrease in size, surfactant concentration is increased, helping prevent the alveoli from collapsing
- reduces the muscular force needed to expand the lungs (i.e. decreases the work of breathing)
- lowers the elastic recoil at low lung volumes and thus helps to prevent the alveoli from collapsing at the end of each expiration

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Endothelin

Endothelin is a potent, long-acting vasoconstrictor and bronchoconstrictor. It is secreted initially as a prohormone by the vascular endothelium and later converted to ET-1 by the action of endothelin converting enzyme. It acts via interaction with a G-protein linked to phospholipase C leading to calcium release. Endothelin is thought to be important in the pathogenesis of many diseases including primary pulmonary hypertension (endothelin antagonists are now used), cardiac failure, hepatorenal syndrome and Raynaud's

Promotes release

- angiotensin II
- ADH
- hypoxia
- mechanical shearing forces

Inhibits release

- nitric oxide
- prostacyclin

Raised levels in

- MI
- heart failure
- ARF
- asthma
- primary pulmonary hypertension

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Questions

Lab Values, Normal Adult: Laboratory...

antibiotics classification chart - Googl...

Pulmonary arteries 42%

Pulmonary arteries vasoconstrict in the presence of hypoxia

Discuss

Improve

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Respiratory physiology: hypoxia

A fall in the partial pressure of oxygen in the blood leads to vasoconstriction of the pulmonary arteries. This allows blood to be diverted to better aerated areas of the lung and improves the efficiency of gaseous exchange

Next question >

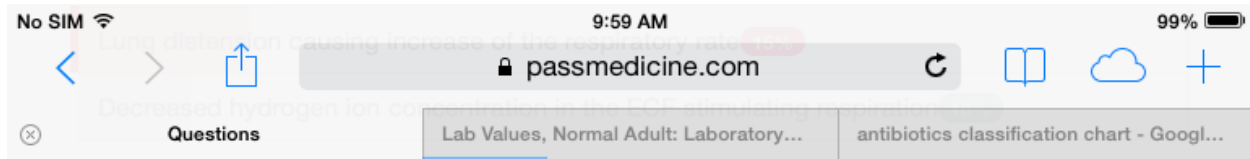
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Respiratory physiology: control

Control of respiration

- central regulatory centres
- central and peripheral chemoreceptors
- pulmonary receptors

Central regulatory centres

- medullary respiratory centre
- apneustic centre (lower pons)
- pneumotaxic centre (upper pons)

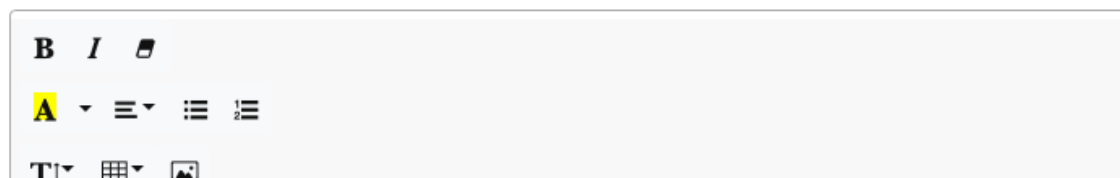
Central and peripheral chemoreceptors

- central: raised $[H^+]$ in ECF stimulates respiration
- peripheral: carotid + aortic bodies, respond to raised pCO_2 & $[H^+]$, lesser extent low pO_2

Pulmonary receptors

- stretch receptors, lung distension causes slowing of respiratory rate (Hering-Bruer reflex)
- irritant receptor, leading to bronchoconstriction
- juxta-capillary receptors, stimulated by stretching of the microvasculature

Next question >



Pneumonectomy 24%



Next question >

Respiratory physiology: lung compliance

Lung compliance is defined as change in lung volume per unit change in airway pressure

Causes of increased compliance

- age
- emphysema - this is due to loss alveolar walls and associated elastic tissue

Causes of decreased compliance

- pulmonary oedema
- pulmonary fibrosis
- pneumonectomy
- kyphosis

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Respiratory physiology

Chloride shift

- CO₂ diffuses into RBCs
- CO₂ + H₂O $\xrightarrow{\text{carbonic anhydrase}}$ HCO₃⁻ + H⁺
- H⁺ combines with Hb
- HCO₃⁻ diffuses out of cell, - Cl⁻ replaces it

Bohr effect

- increasing acidity (or pCO₂) means O₂ binds less well to Hb

Haldane effect

- increase pO₂ means CO₂ binds less well to Hb

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Relevant to my revision >

Less relevant >

Appendicitis in children

Appendicitis is one of the most common acute surgical problems facing children. Diagnosis is often made difficult by a presentation which is far from the classically history of:

- central abdominal pain which later radiates to the right iliac fossa
- low-grade pyrexia
- minimal vomiting

Children who are younger or have a retrocaecal/pelvic appendix are more likely to present in an atypical way

Appendicitis is uncommon in children under 4 years old but in this group often presents with perforation

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Wilms' tumour

Wilms' nephroblastoma is one of the most common childhood malignancies. It typically presents in children under 5 years of age, with a median age of 3 years old.

Features

- abdominal mass (most common presenting feature)
- painless haematuria
- flank pain
- other features: anorexia, fever
- unilateral in 95% of cases
- metastases are found in 20% of patients (most commonly lung)

Associations

- Beckwith-Wiedemann syndrome
- as part of WAGR syndrome with Aniridia, Genitourinary malformations, mental Retardation
- hemihypertrophy
- around one-third of cases are associated with a loss-of-function mutation in the WT1 gene on chromosome 11

Management

- nephrectomy
- chemotherapy
- radiotherapy if advanced disease
- prognosis: good, 80% cure rate



Vitamin deficiency

The table below summarises vitamin deficiency states

Vitamin	Chemical name	Deficiency state
A	Retinoids	Night-blindness (nyctalopia)
B1	Thiamine	Beriberi - polyneuropathy, Wernicke-Korsakoff syndrome - heart failure
B3	Niacin	Pellagra - dermatitis - diarrhoea - dementia
B6	Pyridoxine	Anaemia, irritability, seizures
B7	Biotin	Dermatitis, seborrhoea
B9	Folic acid	Megaloblastic anaemia, deficiency during pregnancy - neural tube defects
B12	Cyanocobalamin	Megaloblastic anaemia, peripheral neuropathy
C	Ascorbic acid	Scurvy - gingivitis - bleeding
D	Ergocalciferol, cholecalciferol	Rickets, osteomalacia
E	Tocopherol, tocotrienol	Mild haemolytic anaemia in newborn infants, ataxia, peripheral neuropathy

		dementia
B6	Pyridoxine	Anaemia, irritability, seizures
B7	Biotin	Dermatitis, seborrhoea
B9	Folic acid	Megaloblastic anaemia, deficiency during pregnancy - neural tube defects
B12	Cyanocobalamin	Megaloblastic anaemia, peripheral neuropathy
C	Ascorbic acid	Scurvy - gingivitis - bleeding
D	Ergocalciferol, cholecalciferol	Rickets, osteomalacia
E	Tocopherol, tocotrienol	Mild haemolytic anaemia in newborn infants, ataxia, peripheral neuropathy
K	Naphthoquinone	Haemorrhagic disease of the newborn, bleeding diathesis

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The effects of vitamin D on osteoblasts are complex and not fully understood. Inhibition of osteoblastic activity would not however be in keeping with a beneficial effect on osteoporosis.




Next question >

Vitamin D

Vitamin D is a fat soluble vitamin that plays a key role in calcium and phosphate metabolism.

Sources

- vitamin D2 (ergocalciferol): plants
- vitamin D3 (cholecalciferol): dairy products, can be synthesised by the skin from sunlight

Functions

- increases plasma calcium and plasma phosphate
- increases renal tubular reabsorption and gut absorption of calcium
- increases osteoclastic activity
- increases renal phosphate reabsorption

Consequences of vitamin D deficiency:

- rickets: seen in children
- osteomalacia: seen in adults

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Vitamin B6 (pyridoxine)

Vitamin B6 is a water soluble vitamin of the B complex group. It is converted to pyridoxal phosphate (PLP) which is a cofactor for many reactions including transamination, deamination and decarboxylation.

Causes of vitamin B6 deficiency

- isoniazid therapy

Consequences of vitamin B6 deficiency

- peripheral neuropathy
- sideroblastic anemia

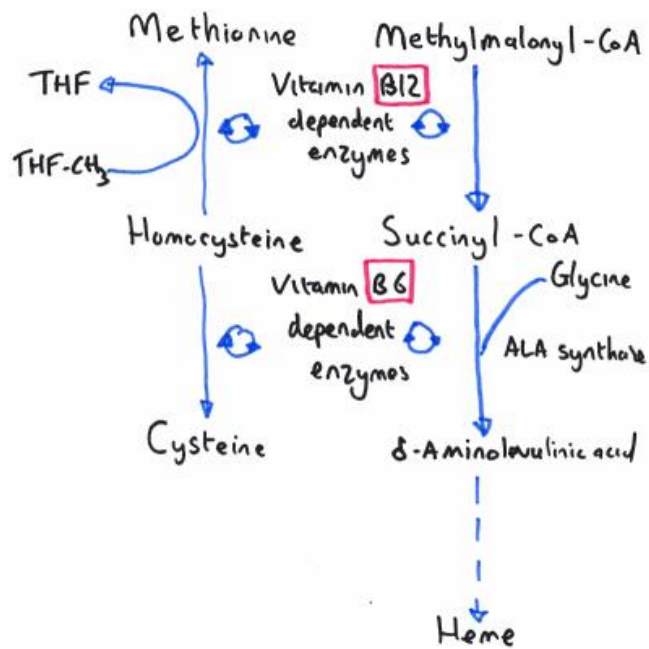


Diagram showing the biochemical role of vitamin B12 and vitamin B6

Next question >

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Questions Lab Values, Normal Adult: Laboratory Reference Ranges in H...

Sarcoidosis 3%

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Vitamin C (ascorbic acid)

Vitamin C is a water soluble vitamin.

Functions

- antioxidant
- collagen synthesis: acts as a cofactor for enzymes that are required for the hydroxylation proline and lysine in the synthesis of collagen
- facilitates iron absorption
- cofactor for norepinephrine synthesis

Vitamin C deficiency (scurvy) leads to defective synthesis of collagen resulting in capillary fragility (bleeding tendency) and poor wound healing

Features vitamin C deficiency

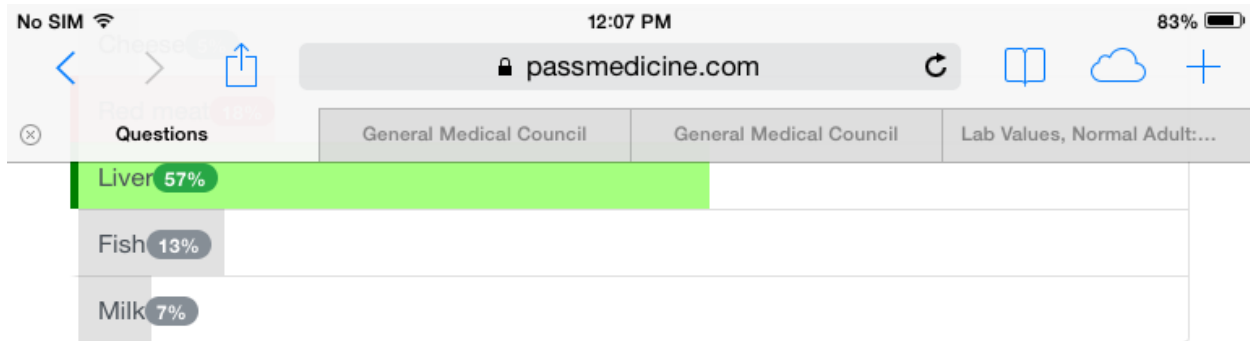
- gingivitis, loose teeth
- poor wound healing
- bleeding from gums, haematuria, epistaxis
- general malaise

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Folic acid is also present in green vegetables and nuts

  Discuss (2) Improve

Next question >

Folate metabolism

Drugs which interfere with metabolism

- trimethoprim
- methotrexate
- pyrimethamine

Drugs which can reduce absorption

- phenytoin

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Vitamin B1 (thiamine)

Thiamine is a water soluble vitamin of the B complex group. One of its phosphate derivatives, thiamine pyrophosphate (TPP), is a coenzyme in the following enzymatic reactions:

- pyruvate dehydrogenase complex
- pyruvate decarboxylase in ethanol fermentation
- alpha-ketoglutarate dehydrogenase complex
- branched-chain amino acid dehydrogenase complex
- 2-hydroxyphytanoyl-CoA lyase
- transketolase

Thiamine is therefore important in the catabolism of sugars and aminoacids. The clinical consequences of thiamine deficiency are therefore seen first in highly aerobic tissues such as the brain (Wernicke-Korsakoff syndrome) and the heart (wet beriberi).

Causes of thiamine deficiency:

- alcohol excess
- malnutrition

Conditions associated with thiamine deficiency:

- Wernicke's encephalopathy: nystagmus, ophthalmoplegia and ataxia
- Korsakoff's syndrome: amnesia, confabulation
- dry beriberi: peripheral neuropathy
- wet beriberi: dilated cardiomyopathy

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Close

Alkaline phosphatase is significantly elevated in pregnancy. This would also explain the borderline anaemia



 Discuss (10) Improve

Next question >

Alkaline phosphatase

Causes of raised alkaline phosphatase (ALP)

- liver: cholestasis, hepatitis, fatty liver, neoplasia
- Paget's
- osteomalacia
- bone metastases
- hyperparathyroidism
- renal failure
- physiological: pregnancy, growing children, healing fractures

The table below splits the causes according to the calcium level

Raised ALP and raised calcium	Raised ALP and low calcium
Bone metastases Hyperparathyroidism	Osteomalacia Renal failure

Next question >

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Questions
General Medical Council
General Medical Council
Lab Values, Normal Adult:...

There is no need to retake the driving test in this scenario.

Discuss

Improve

Next question >

DVLA: visual disorders

The guidelines below relate to car/motorcycle use unless specifically stated. For obvious reasons, the rules relating to drivers of heavy goods vehicles tend to be much stricter

Visual field defects

- driving must cease unless confirmed able to meet recommended national guidelines for visual field

Monocular vision

- must notify DVLA
- may drive if acuity and visual field is normal in the remaining eye

Blepharospasm

- consultant opinion is required

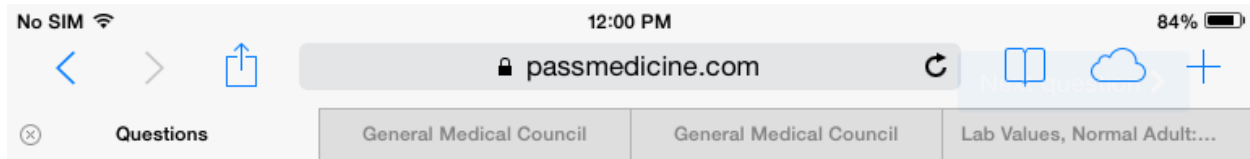
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Fitness to fly

The Civil Aviation Authority (CAA) has issued guidelines on air travel for people with medical conditions; please see the link provided.

Cardiovascular disease

- unstable angina, uncontrolled hypertension, uncontrolled cardiac arrhythmia, decompensated heart failure, severe symptomatic valvular disease: should not fly
- uncomplicated myocardial infarction: may fly after 7-10 days
- complicated myocardial infarction: after 4-6 weeks
- coronary artery bypass graft: after 10-14 days
- percutaneous coronary intervention: after 5 days

Respiratory disease

- pneumonia: should be 'clinically improved with no residual infection'
- pneumothorax: absolute contraindication, the CAA suggest patients may travel 2 weeks after successful drainage if there is no residual air. The British Thoracic Society used to recommend not travelling by air for a period of 6 weeks but this has now been changed to 1 week post check x-ray

Pregnancy

- most airlines do not allow travel after 36 weeks for a single pregnancy and after 32 weeks for a multiple pregnancy
- most airlines require a certificate after 28 weeks confirming that the pregnancy is progressing normally

Surgery

- travel should be avoided for 10 days following abdominal surgery
- laparoscopic surgery: after 24 hours
- colonoscopy: after 24 hours
- following the application of a plaster cast, the majority of airlines restrict flying for 24 hours on flights of less than 2 hours or 48 hours for longer flights

Haematological disorders

- patients with a haemoglobin of greater than 8 g/dl may travel without problems (assuming there is no coexisting condition such as cardiovascular or respiratory disease)

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Questions

Lab Values, Normal Adult: Laboratory...

antibiotics classification chart - Googl...

Discuss (2)

Improve

Next question >

Epidermis

The epidermis is the outermost layer of the skin and is composed of a stratified squamous epithelium with an underlying basal lamina

It may be divided in to five layers:

Layer	Description
Stratum corneum	Flat, dead, scale-like cells filled with keratin Continually shed
Stratum lucidum	Clear layer - present in thick skin only
Stratum granulosum	Cells form links with neighbours
Stratum spinosum	Squamous cells begin keratin synthesis Thickest layer of epidermis
Stratum germinativum	The basement membrane - single layer of columnar epithelial cells Gives rise to keratinocytes Contains melanocytes

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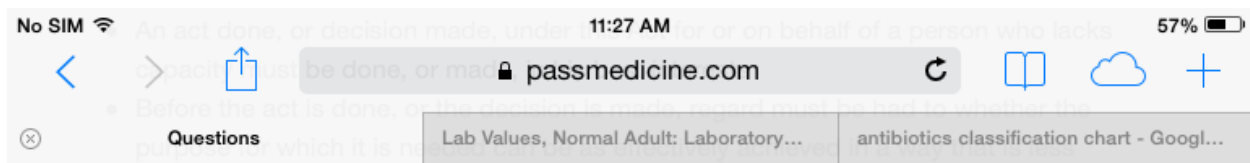
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restrictive of the person's rights and freedom of action



Next question >

Patients who refuse treatment

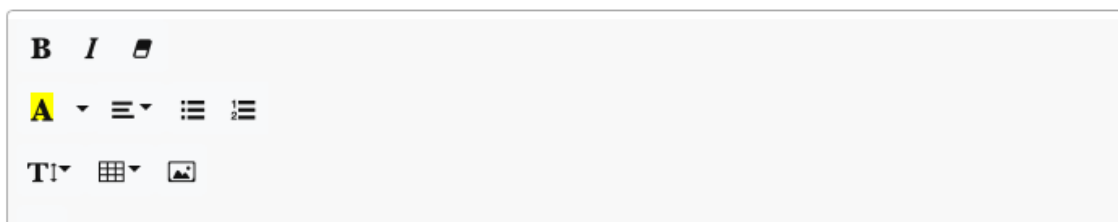
Many patients who are admitted to hospital, or treated in the community, lack capacity. In the vast majority of cases, these patients do not refuse treatment that is given that is deemed to be in their best interest. The problem arises when patients who lack (or are suspected of lacking) capacity refuse treatment.

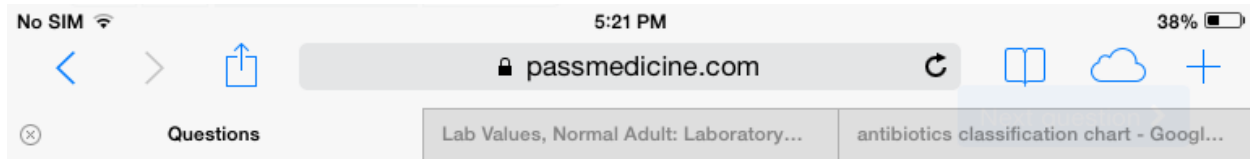
There are 3 main frameworks that are used in this scenario:

- common law: used to treat patients in **emergency scenarios**
- Mental Capacity Act: (MCA) used in patients who require treatment **physical disorders** that affect brain function. Remember this may be delirium secondary to sepsis or a primary brain disorder such as dementia
- Mental Health Act (MHA): used in patients who require treatment for **mental disorders**. For patients already admitted to hospital, a section 5(2) is used if there is not the time for a more formal section 2 or 3. A typical scenario would be a patient who has a mental health disorder attempting to discharge themselves, when it is thought this may result in harm

An excellent, more in-depth review can be found in the BMJ 'When and how to treat patients who refuse treatment'. BMJ 2014;348:g2043

Next question >





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Next question >

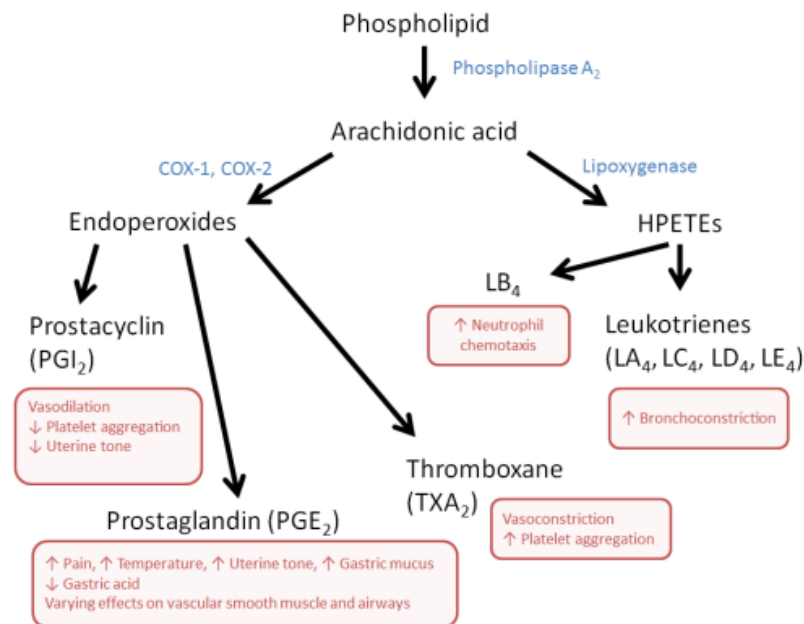
Prolactin

	Notes	Further detail
Source	Anterior pituitary	
Function	Stimulates breast development (both initially and further hyperplasia during pregnancy) Stimulates milk production It decreases GnRH pulsatility at the hypothalamic level and to a lesser extent, blocks the action of LH on the ovary or testis.	
Regulation	Prolactin secretion is under constant inhibition by dopamine Increases secretion • thyrotropin releasing hormone • pregnancy • oestrogen • breastfeeding • sleep • stress • drugs e.g. metoclopramide, antipsychotics Decreases secretion • dopamine • dopaminergic agonists	

Next question >

Arachidonic acid metabolism

The diagram below shows the metabolism of arachidonic acid:



Leukotrienes

- LTB4: B4 (before) leukocytes comes LTB4
- the rest A, C, D & E constrict the lungs

Endoperoxides

- THROMBOXane think THROMBOSIS: platelets aggregated and vasoconstriction. Prostacyclin is the opposite

Disorders of sex hormones

The table below summarises the findings in patients who have disorders of sex hormones:

Disorder	LH	Testosterone
Primary hypogonadism (Klinefelter's syndrome)	High	Low
Hypogonadotrophic hypogonadism (Kallman's syndrome)	Low	Low
Androgen insensitivity syndrome	High	Normal/high
Testosterone-secreting tumour	Low	High

Klinefelter's syndrome

Klinefelter's syndrome is associated with karyotype 47, XXY

Features

- often taller than average
- lack of secondary sexual characteristics
- small, firm testes
- infertile
- gynaecomastia - increased incidence of breast cancer
- elevated gonadotrophin levels

Diagnosis is by chromosomal analysis

Kallman's syndrome

Kallman's syndrome is a recognised cause of delayed puberty secondary to hypogonadotrophic hypogonadism. It is usually inherited as an X-linked recessive trait. Kallman's syndrome is thought to be caused by failure of GnRH-secreting neurons to migrate to the hypothalamus.

The clue given in many questions is lack of smell (anosmia) in a boy with delayed puberty

Features

- 'delayed puberty'
- hypogonadism, cryptorchidism
- anosmia
- sex hormone levels are low

Pass

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Features

- 'delayed puberty'
- hypogonadism, cryptorchidism
- anosmia
- sex hormone levels are low
- LH, FSH levels are inappropriately low/normal
- patients are typically of normal or above average height

Cleft lip/palate and visual/hearing defects are also seen in some patients

Androgen insensitivity syndrome

Androgen insensitivity syndrome is an X-linked recessive condition due to end-organ resistance to testosterone causing genotypically male children (46XY) to have a female phenotype. Complete androgen insensitivity syndrome is the new term for testicular feminisation syndrome

Features

- 'primary amenorrhoea'
- undescended testes causing groin swellings
- breast development may occur as a result of conversion of testosterone to oestradiol

Diagnosis

- buccal smear or chromosomal analysis to reveal 46XY genotype

Management

- counselling - raise child as female
- bilateral orchidectomy (increased risk of testicular cancer due to undescended testes)
- oestrogen therapy